Anakinra and canakinumab for patients with R92Q-associated autoinflammatory syndrome: a multicenter observational study from the AIDA Network

Ther Adv Musculoskel Dis

2021, Vol. 13: 1–11

DOI: 10.1177/1759720X211037178

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Abstract

Background: This study aims at describing the therapeutic outcome of patients carrying the R92Q variant in the *TNFRSF1A* gene treated with anakinra (ANA) or canakinumab (CAN) and identifying any factors predictive of complete response to IL-1 inhibition.

Methods: Clinical data of patients treated with ANA or CAN for recurrent inflammatory attacks due to the presence of the R92Q variant were retrospectively collected and analysed.

Results: Data about 20 treatment courses with IL-1 inhibitors (16 with ANA and 4 with CAN) from 19 patients were collected. Mean age at disease onset was 20.2 ± 14.8 years. In 5 cases (26%) the R92Q variant was found in a family member affected by recurrent fever. The therapeutic response was complete in 13(68%) and partial in 2 patients (11%); treatment failure was observed in 4 cases (21%). Median AIDAI decreased from 10 (interquartile range [IQR] = 28) to 0 (IQR = 1) at the 12-month follow-up visit ($p < 0.001$). Mean ESR and median CRP dropped respectively from 40.8 ± 24.8 to 9.1 ± 4.5 mm/h ($p < 0.001$) and from 3.0 (IQR = 1.9) to 0.3 (IQR = 0.3) mg/dl ($p < 0.001$) after 12 months of treatment. A steroid-sparing effect was observed from the third month of treatment ($p < 0.01$). Thirteen patients (65%) were still on treatment at the last follow-up visit (median duration of treatment 17 (IQR = 38) months). The presence of R92Q mutation in a symptomatic relative ($p = 0.022$), the relapsing remitting disease course ($p < 0.001$) and the presence of migratory erythematous skin rashes during fever attacks ($p = 0.005$) were associated with complete efficacy of IL-1 inhibitors.

Conclusions: R92Q patients showed a favourable response to ANA and CAN, particularly when the mutation segregated in a family member and when a relapsing-remitting disease course or TNF-α receptor-associated periodic syndrome (TRAPS) typical skin rash were observed. In the subgroup of patients not taking advantage of IL-1 blockage different molecular mechanisms underlying the autoinflammatory picture are likely to exist.

Keywords: anakinra, biologic therapy, canakinumab, innovative biotechnologies, interleukin-1 inhibition, personalized medicine, R92Q variant, TNF-α receptor associated periodic syndrome

Received: 22 February 2021; revised manuscript accepted: 16 July 2021.

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Introduction

Mutations in the *TNFRSF1A* gene encoding for tumour necrosis factor-α (TNF-α) receptor type 1 are known to cause the autosomal dominant autoinflammatory syndrome named TNF-α receptor-associated periodic syndrome (TRAPS). The syndrome is characterized by a relapsing-remitting course with recurrent fever attacks lasting several days associated with skin rash, myalgia, abdominal pain, periorbital edema, articular involvement and other inflammatory symptoms; otherwise the course of the disease can be chronic with continuous symptoms and/or steadily elevated inflammatory markers.[1,2] A wide spectrum of phenotypic variability has been described in patients carrying *TNFRSF1A* variants, ranging from the asymptomatic to the most severe forms of TRAPS, which might lead to development of systemic amyloidosis.[3] Structural mutations are often localized on exons 2, 3 and 4 and affect highly preserved cysteine residues, necessary for the stability of disulphide bonds within the extracellular domain of the protein. Interrupting the folding of the extracellular portion of the receptor, these mutations generally lead to a severe disease phenotype with higher risk of AA amyloidosis.[4] Among low-penetrance variants, R92Q located within exon 4 represents one of the most common mutations found in TRAPS patients. It is associated with a variable but usually mild autoinflammatory phenotype, with late disease onset, weaker familial association, negligible risk of amyloidosis, shorter fever attacks and higher rate of spontaneous resolution compared to structural mutations.[1,5] Oligosymptomatic or atypical phenotypes, including idiopathic recurrent acute pericarditis, have been described as R92Q carriers as well.[6,7] Moreover, R92Q frequency is around 1–5.2% in different populations, and in some cases the mutation does not even segregate within the TRAPS phenotype, to the point that it has been considered a functional polymorphism.[3,8–10] Also, it has been identified at a higher frequency in patients with multifactorial inflammatory conditions such as periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) syndrome, early arthritis, juvenile idiopathic arthritis, vasculo-Behçet's disease, idiopathic recurrent pericarditis and multiple sclerosis, compared to healthy subjects.[10–15] For these reasons, the R92Q mutation is still classified among variants of uncertain significance (Infevers: an online database for autoinflammatory mutations. Available at https://infevers.umai-montpellier.fr/ Accessed (2020.12.13)).[16]

The gold standard treatment of TRAPS is the inhibition of interleukin (IL)-1, a pro-inflammatory cytokine which plays a pleiotropic role in innate immunity. Although key aspects of the pathogenesis of the disease still have to be clarified, IL-1 has been recognized as the final effector of the stress-response mechanisms activated by the deregulated cellular homeostasis in TRAPS patients.[17–20] Indeed, several studies reported a striking efficacy of the IL-1 blockers anakinra (ANA) and canakinumab (CAN) in the treatment of TRAPS, including phase II and III trials leading to the registration of CAN by the European Medicines Agency (EMA) for this indication.[21–24] Given the uncertainty about the molecular mechanism and pathogenic significance of the R92Q variant in TRAPS, the therapeutic response to IL-1 inhibitors in patients with recurrent inflammatory attacks due to the presence of this specific mutation is worth an extensive investigation.

Aims of the study

Primary aim of this study was to describe the therapeutic outcome of patients carrying the R92Q variant in the *TNFRSF1A* gene treated with ANA or CAN for their autoinflammatory condition.

Secondary aim was to identify among clinical and laboratory features at disease onset any factors predictive of complete response to IL-1 inhibition.

Patients and methods

This is an observational retrospective multicentre study involving 13 tertiary referral centres in Italy, Spain, Poland, Belgium and Egypt contributing to the AutoInflammatory Disease Alliance (AIDA) Network.

Adult and paediatric patients ever treated with ANA or CAN for inflammatory attacks due to the presence of the R92Q variant in the *TNFRSF1A* gene were included in the study, disregarding the fulfilment of the classification criteria for TRAPS.[25] The presence of other gene mutations better explaining the clinical phenotype was an exclusion criterion. The diagnosis of a defined multifactorial autoinflammatory disease according to the relative diagnostic criteria, including PFAPA syndrome, systemic juvenile idiopathic arthritis, adult-onset Still's disease, Behçet's

syndrome and others, was considered an exclusion criterion as well.

Demographic, clinical, laboratory, clinimetric and therapeutic data of each patient were collected retrospectively based on clinical charts by the treating physician. Timepoints for data collection were set at the time of disease onset, at the time of diagnosis, at the start of treatment with IL-1 inhibitors, at 1-, 3-, 6- and 12 months of follow-up, and at the last assessment. Classification scores for TRAPS were derived by the authors on the basis of available data.[25]

Disease activity was measured through the AIDAI score, as recommended internationally to standardize outcome measurements, and thus improve comparisons between studies on autoinflammatory diseases.[26] The AIDAI score is a numeric index resulting from the sum of the symptoms reported day by day (as present or absent) by the patient over a 29-day period.[27] It is the only validated disease activity index for TRAPS, since it has been demonstrated capable of discriminating clinically active (score ≥ 9) from inactive (score < 9) disease. However, not all the clinical charts included the AIDAI score, which has been developed in 2011. Therefore, we decided to include further outcome measures in this study. In detail, the following outcome measures have been assessed: (1) reduction in the AIDAI score at 1-, 3-, 6- and 12 months of treatment;[27] (2) reduction in the level of serum inflammatory markers (C-reactive protein (CRP), erythrocyte sedimentation rate (ESR)) at 1-, 3-, 6- and 12 months of treatment; (3) steroid-sparing effect of the therapy at 1-, 3-, 6- and 12 months (expressed as prednisone equivalent); (4) a physician global assessment of the therapeutic response, defined as follows. The global therapeutic response was considered 'complete' if the treatment induced a total control of symptoms, associated with the normalization of inflammatory markers (CRP, ESR and serum amyloid-A (SAA)); the response was defined 'partial' if (1) a reduction of symptom severity occurred during attacks or between flares for patients with relapsing-remitting or chronic disease course, respectively, or if (2) a reduction of the level of inflammatory markers during febrile attacks was observed, without reaching normal values; the therapeutic response was considered 'absent' (primary failure) if none of the previous criteria was satisfied. Therapeutic failure was defined 'secondary' if a clinical relapse was observed during maintenance treatment, several months after complete remission had been achieved.

As for the posology of the IL-1 inhibitors, we defined 'standard dosages' the following ones: ANA 100 mg/day (weight > 50 kg) or 1–2 mg/kg/day (weight < 50 kg); CAN 150 mg (weight > 40 kg) or 2 mg/kg (weight > 40 kg) every 4 weeks.

The study protocol conformed to the tenets of the Declaration of Helsinki and was approved by the local Ethics Committee of the University of Siena (Reference No. 14951). Written informed consent for using clinical data for research purposes was obtained according to the local Institutional review board guidelines. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines for reporting observational studies were followed.[28]

Statistical analysis

Data were analysed using JASP open-source statistics package. Descriptive statistics included sample sizes, mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate. Shapiro-Wilk test was used to assess normality distribution of data. Paired categorical variables were analysed using 2 x 2 contingency tables with Fisher exact test or McNemar's Chi-Square test with Yates' continuity correction, as appropriate. Analysis of means of paired samples was investigated through repeated measures ANOVA test with Greenhouse-Geisser sphericity correction and Bonferroni post hoc analysis, or Friedman's test and Conover's post hoc comparisons, as appropriate. Univariate logistic regression analysis was performed to detect potential factors predictive of complete response to the therapy. The threshold for statistical significance was set to $p < 0.05$ and all p-values were two-sided.

Results

Data about 20 treatment courses from 19 patients treated with ANA or CAN were collected. Mean age at disease onset was 20.2 ± 14.8 years (range: 1–52). In 5 cases (26%), the R92Q variant was found in a family member affected by recurrent fever. In 15 cases (79%), the disease could be classified as TRAPS according to the Eurofever classification criteria. As for the 5 patients not classified as TRAPS according to the current classification criteria, they have been treated with

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IL-1 inhibitors before 2019, when the Eurofever classification criteria that are currently used were not available yet. More in detail, two patients suffered from recurrent pericarditis, which was not controlled by colchicine prophylaxis, leading to the introduction of ANA; one of them had very high levels of serum amyloid A (>1000 mg/L) during attacks. Two further patients had spontaneous febrile attacks associated with abdominal pain, chest pain, myalgia and arthralgia, in one case, and erythematous rash and abdominal pain in the other one; these two patients had a chronic disease course, with steadily elevated inflammatory markers even between febrile attacks, and they were treated with ANA as steroid-sparing agent, since they needed daily use of moderate to high dose prednisone. On the contrary, the last patient was treated with CAN for relapsing-remitting inflammatory attacks of long-lasting fever, myalgia, oral aphthosis, chest and abdominal pain, with elevated ESR (> 100 mm/h) recurring despite colchicine therapy.

Main characteristics of the cohort are summarized in Table 1.

Sixteen patients were treated with ANA and 4 with CAN. One patient stopped ANA therapy after 3 months due to primary failure and was subsequently treated with adalimumab, tocilizumab and CAN. The median duration of therapy was 17 (IQR = 38) months (1–120). The IL-1 inhibitor was administered as first biologic agent in 15 cases (75%) and as second to fourth biologic line of treatment in 5 cases (25%). Patients had been previously treated with non-steroidal anti-inflammatory drugs (NSAIDs) in 18 (90%), oral glucocorticoids in 16 (80%), colchicine in 13 (65%), ANA in 3 (15%), etanercept in 3 (15%), adalimumab in 1 (5%) and tocilizumab in 2 (10%) cases.

The IL-1 inhibitors were employed with standard posology in 19 patients (95%); 1 patient was treated with ANA at a lower attack dose. In 9 cases (45%) the initial dose was adjusted during follow-up based on the individual response, by increasing or decreasing the dose (in 1 and 2 cases, respectively) or by shortening or increasing intervals between administrations (in 2 and 4 cases, respectively).

The overall response to the biologic therapy was complete in 13 (68%), partial in 2 (11%) and absent in 4 patients (21%); for 1 patient (5%) the follow-up on CAN was too short to reliably assess the global therapeutic outcome. Among the 15 patients who satisfied the classification criteria for TRAPS, a complete therapeutic response was achieved in 11 (79%), a partial response in 1 (7%) and no response in 2 cases (14%); among the 5 patients who did not satisfy the classification criteria for TRAPS, a complete therapeutic response was achieved in 2 (40%), a partial response in 1 (20%) and no response in 2 cases (40%) ($p = 0.28$).

The frequency of autoinflammatory features in the cohort at the start of treatment with ANA or CAN and at 1, 3, 6 and 12 months of follow-up is summarized in Table 2.

The median AIDAI[27] decreased from 10 (IQR 28) to 3 (IQR 8) after 1 month of treatment ($p < 0.001$), to 0.5 (IQR 3.3) after 3 months ($p < 0.001$), and to 0 (IQR 2.5) after 6 months ($p < 0.001$) (Figure 1). The mean ESR and the median CRP decreased during 12 months of treatment from 40.8 ± 24.8 to 9.1 ± 4.5 mm/h ($p < 0.001$) and from 3.0 (IQR 1.9) to 0.3 (IQR 0.3) mg/dl ($p < 0.001$), respectively. A significant steroid sparing effect was observed since the third month of biologic therapy, with a mean prednisone dosage of 19.1 ± 19.3 and 4.0 ± 5.7 mg/day at the start of therapy and at 3-month follow-up, respectively ($p = 0.004$) (Figure 1).

The therapy with ANA or CAN was ongoing at the last follow-up visit in 13 patients (65%) and had been withdrawn in 7 cases (35%). Withdrawal was due to primary failure in 3 (15%), primary failure and safety concern in 1 (5%), secondary inefficacy in 1 (5%), and poor compliance despite complete efficacy in 2 cases (10%) (Figure 2). Adverse events were classified as mild in all cases: 2 patients (10%) reported injection site reactions with ANA; 1 patient (5%) had chest tightness leading to ANA discontinuation; 1 further patient (5%) had amnesia with ANA; recurrent cystitis was reported by 1 patient (5%) treated with CAN.

The presence of the R92Q mutation in a symptomatic relative, the relapsing-remitting disease course, and the presence of migratory erythematosus skin rashes during attacks were identified as factors associated with a complete response to the therapy with IL-1 inhibitors ($p = 0.022$, $p < 0.001$ and $p = 0.023$, respectively). No pre-treatment clinical and laboratory features were predictive of the therapeutic response with any statistical significance.

Discussion

TRAPS management is more challenging than in other monogenic autoinflammatory disorders, due to a frank genetic heterogeneity giving rise to protean and complex clinical sceneries. The identification of *TNFRSF1A* mutations as the genetic cause of TRAPS raised the possibility that blocking TNF-α could potentially represent the primary therapeutic strategy,[29] though etanercept, the soluble form of the p75 TNF-α *receptor*, gave conflicting results in real-life experience, differently from the success obtained in other autoinflammatory disorders.[30–32] More recently, anti-IL-1 agents have proved to be reasonable options to prevent TRAPS relapses both in the short- and long-term.[33,34]

The present study describes the therapeutic outcome of patients treated with two IL-1 inhibitors, ANA and CAN, to control febrile relapses in consequence of the R92Q variant in the *TNFRSF1A* gene. The pathogenic significance of this mutation in the context of TRAPS is still unclear.

It has been demonstrated that both the structure and functional behaviour of the protein affected by the R92Q variant is similar to the wild-type TNF-α receptor. Differently from what is demonstrated for structural mutations, neither accumulation of misfolded receptors in the cytoplasm, nor altered expression in cell membranes, nor defective shedding of the receptor–which are the mechanisms responsible of the increased production of IL-1 and the downstream pro-inflammatory cascade in TRAPS patients–have been observed.[17,18,35,36] According to this view, patients with an autoinflammatory phenotype due to the presence of R92Q may be expected to exhibit a different response rate to IL-1 blockade than that documented in patients with structural TRAPS-related mutations.

It has been observed that R92Q-positive patients are successfully treated with NSAIDs, colchicine or glucocorticoids as monotherapy more frequently than those with different mutations of the same gene, probably due to the reduced expressivity of this variant.[37–39] Nevertheless, recent data gathered from the AIDA cohort disclose that the percentage of R92Q patients requiring cytokine blockers is up to 53%, surprisingly higher than previously reported.[39–43] In the present study, the efficacy rate of ANA and CAN was 68%, being 'complete efficacy' defined as the resolution of symptoms and normalization of

Table 1. Demographic characteristics of the cohort and details of the therapeutic courses with IL-1 inhibitors.

Number of treatment courses (ANA: CAN)	**20 (16:4)**
Male: female	8:11
Current age, years	
mean ± SD	36.5 ± 15.6
(range)	(19–66)
Detection of R92Q variant in relatives affected by recurrent fever	5 (26%)
Age at onset, years	
mean ± SD	20.2 ± 14.8
(range)	(1–52)
Age at diagnosis, years	
median (IQR)	25 (17.5)
(range)	(12–57)
Diagnostic delay, years	
median (IQR)	5.0 (6.5)
(range)	(1–28)
Disease course before the start of IL-1 inhibitors	
Relapsing-remitting	14 (70%)
Chronic	6 (30%)
Classification as TRAPS according to	
Eurofever criteria for TRAPS[25]	15 (79%)
Eurofever clinical criteria for TRAPS[25]	9 (47%)
Duration of the therapy with IL-1 inhibitors, months	
median (IQR)	17.0 (38)
(range)	(1–120)
Duration of follow-up, years	
median (IQR)	5 (9.5)
(range)	(2–36)
Line of biologic treatment	
First	15 (75%)
Second (or further)	5 (25%)
Previous therapies	
NSAIDs	18 (90%)
Oral glucocorticoids	16 (80%)

(Continued)

Table 1. (Continued)

Number of treatment courses (ANA: CAN)	20 (16:4)
Colchicine	13 (65%)
Anakinra	3 (15%)
Etanercept	3 (15%)
Adalimumab	1 (5%)
Tocilizumab	2 (10%)

ANA, anakinra; CAN, canakinumab; IL, interleukin; IQR, interquartile range; NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation; TRAPS, TNF-α receptor-associated periodic syndrome.

ESR, CRP and SAA, which should demonstrate the absence of both manifest and subclinical inflammation. Accordingly, the median AIDAI score, which measures the clinical activity of the disease, was significantly lower at month-1 follow-up visit, while mean values of laboratory markers of inflammation decreased more slowly reaching the statistical significance after 3 months of treatment. Both clinical and serological parameters were adequately controlled up to 12 months of follow-up; moreover, more than two-thirds of our cohort were still on IL-1 inhibition at their last visit.

Few heterogeneous data about the therapeutic outcome of IL-1 inhibitors in R92Q-positive patients can be derived from most studies available in the medical literature. The 'umbrella' trial leading to the registration of CAN for TRAPS involved 15 patients carrying the R92Q mutation (equal to 33% of the study group); CAN displayed a complete efficacy at week 16 in 45% of patients (73% including those treated with increased dosage), but the genotype of responders/not responders was not detailed in the paper.[22] Among the 5 patients affected by TRAPS successfully treated with ANA in a 2008 prospective, one carried the R92Q variant showing a chronic disease course with fluctuating symptoms and persistent elevation of acute-phase reactants; he had a favourable response to ANA, leading to discontinuation of the concomitant anti-inflammatory therapy.[21] Data from case reports and case series of R92Q-positive patients undergoing ANA or CAN are controversial, reporting both success and failure of IL-1 inhibition;[44–48] moreover, this level of evidence is usually affected by publication bias which may negatively impact on the number of therapeutic failures reported in the literature.

In the cohort described by the present study, the presence of the R92Q mutation in a relative affected by recurrent fever, the presence of migratory erythematosus skin rashes during attacks and the relapsing-remitting disease course were associated with a complete therapeutic response to ANA and CAN with statistical significance. The percentage of patients inheriting R92Q from a relative affected by recurrent fever was consistent with that previously reported in other TRAPS cohorts, although no data about the possible association between familial segregation and response to IL-1 inhibition are available in the literature to date.[5,8] It is worth mentioning that two out of three of the variables associated to ANA and CAN complete efficacy in this study are included in the TRAPS classification score, although a direct association between the fulfilment of classification criteria and therapeutic outcome was not found. In a recent retrospective study based on the Eurofever cohort, ANA was efficacious in 7 patients out of 10 (70%) carrying variants of uncertain significance or not classified (VUS/NC) according to International Study Group for Systemic Autoinflammatory Diseases (INSAID) classification. The study group included both well-known low penetrance mutations such as R92Q and non classified variants, involving cysteine residues on the exons 3 and 4, making data too heterogeneous to compare. Nevertheless, of particular relevance to our results, this paper argues that the fulfilment of TRAPS classification criteria within the group of subjects carrying VUS/NC mutations would identify a subset of patients who display a better response to biologics.[49] Therefore, our data support the increasing evidence that, when R92Q is detected in patients whose clinical phenotype clearly resembles TRAPS, IL-1 inhibitors can be considered the therapy of choice, if a therapeutic step up is needed due to the frequency and intensity of flares. However, these considerations should be taken with caution given the retrospective design of the study, the low number of data and the absence of a clear predictive value of the variables associated with therapeutic success.

From a different point of view, the 32% failure rate of IL-1 inhibitors in our cohort (either complete inefficacy or partial improvement of symptoms and laboratory parameters) discloses the predominance of molecular pathways not directly related to IL-1 as main pathogenic drivers of autoinflammation in the non-responder group. In

Table 2. Frequency of clinical manifestations at the start of treatment with IL-1 inhibitors and after 1, 3, 6 and 12 months of therapy.

	Chest pain	Pharyngitis	Oral aphthosis	Skin rash	Pericarditis	Lymphoadenitis	Abdominal pain	Myalgia	Arthralgia	Arthritis	Conjunctivitis	Periorbital edema
Baseline	8 (40%)	8 (40%)	7 (35%)	9 (45%)	6 (30%)	6 (30%)	11 (55%)	14 (70%)	15 (75%)	6 (30%)	3 (15%)	0
Month-1	**2* (10%)**	**0***	**0***	2 (10%)	1 (5%)	2 (10%)	4 (20%)	**3** (15%)**	7 (35%)	1 (5%)	0	0
Month-3	**0***	**0***	**0***	**1* (5%)**	**0***	1 (5%)	**2* (10%)**	**0****	**4* (20%)**	0	0	0
Month-6	1 (5%)	2 (10%)	**0***	1 (5%)	**0***	1 (5%)	1 (5%)	**1** (5%)**	**4* (20%)**	0	0	1 (5%)
Month-12	2 (10%)	3 (15%)	**0***	1 (5%)	1 (5%)	2 (10%)	1 (5%)	**2* (10%)**	**4* (20%)**	0	0	1 (5%)

Statistical significance is referred to the comparison of each timepoint with the baseline assessment: $^{*}p < 0.05$ $^{**}p < 0.01$.

the clinical setting, these patients should be carefully reassessed and eventually undergo further investigations to rule out diagnoses other than TRAPS. It is the authors' opinion that both extended genetic analysis and gene expression profile studies may be warranted after failure of IL-1 inhibitors in R92Q-positive patients showing a clear autoinflammatory phenotype. *In silico* data suggest that the R92Q variant modifies the energy of interaction between different domains of the amino acid chain;[50] this would affect the configuration and the molecular dynamics of the mutated receptor after binding to its ligand, inducing an increased or decreased bend angle, according to different studies.[50,51] Studies on gene expression profiles of cells transfected with the R92Q variant revealed clustering of transcripts specifically altered in mutants compared with wild-type transfectants, and with a clear separation also from the cysteine mutant transfectants.[52] Functional analysis of blood samples from R92Q carriers found an increased plasmatic level of monocyte chemoattractant protein-1 (MCP-1/CCL2) and TNF-induced IL-12p70 release.[11] Whether such molecular effects are sufficient to cause an autoinflammatory picture by themselves is still being discussed and the phenotypic variability of R92Q patients does not yet offer a clear pathophysiological explanation. A recent concept hypothesizes a synergic pro-inflammatory function of R92Q in a context of oligogenic transmission, intermediate in the continuum from monogenic to multifactorial polygenic inheritance: the affected individual would inherit multiple low-frequency allele variants that act synergistically in determining the clinical picture.[53]

Conclusion

This study describes the therapeutic outcome of the largest cohort of R92Q patients treated with IL-1 inhibitors so far in the literature. More than two-thirds of them showed complete response to the therapy and retained the drugs up to the last follow-up visit, with a median treatment duration of 17 months. In the responder group, the presence of clinical manifestations typical of TRAPS (i.e. the erythematous migrating skin rash), the relapsing-remitting disease course and the segregation of the mutation in the family of the proband were significantly more frequent, although no predictive value was observed for any of these factors. In the subgroup of patients not taking advantage of IL-1 blockade different molecular

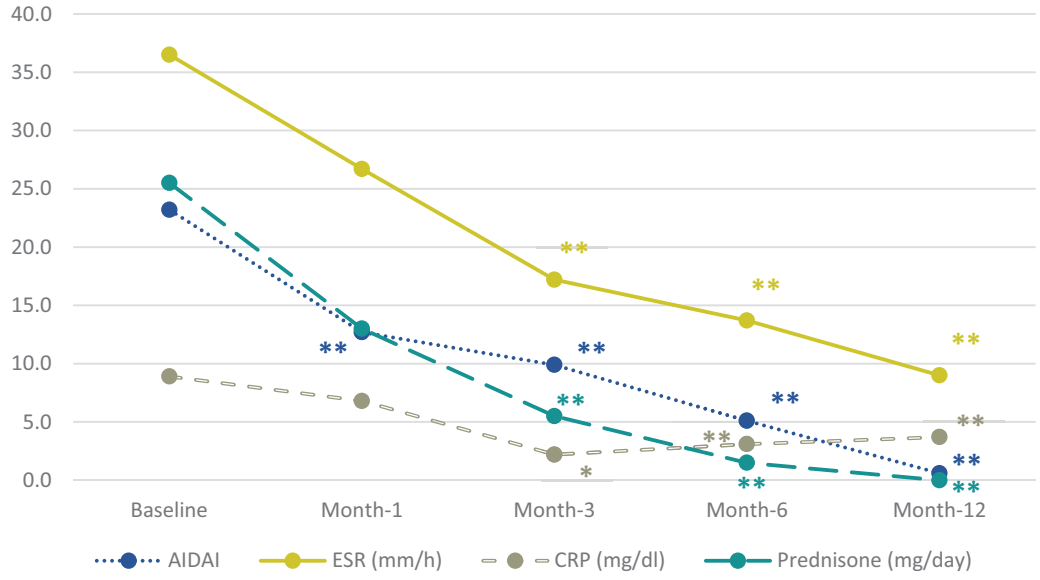

Figure 1. Time variation over 12 months of the AIDAI score, glucocorticoid need and serum values of inflammatory markers during IL-1 inhibitor therapy.
Statistical significance is referred to the comparison of each timepoint with the baseline assessment: $*p < 0.05$ $**p < 0.01$.
AIDAI, autoinflammatory disease activity index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

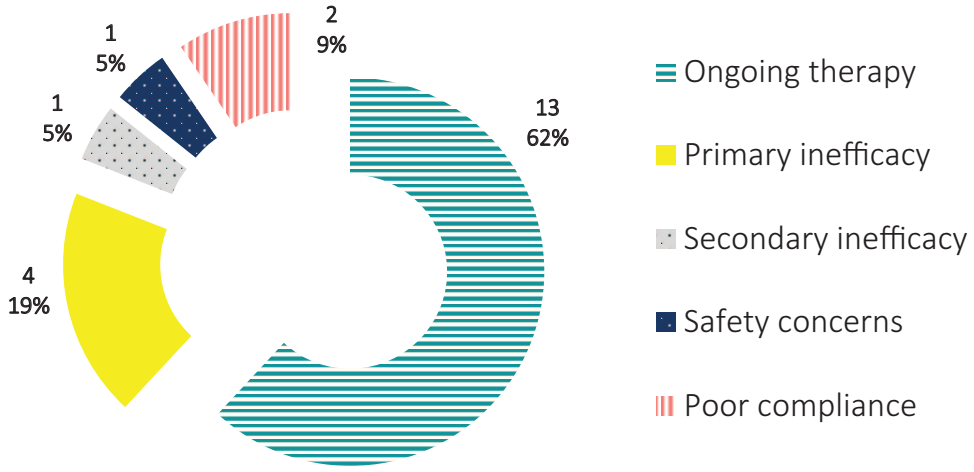

Figure 2. Number and percentage of patients still on therapy or having discontinued IL-1 inhibitors due to primary inefficacy, secondary inefficacy, safety concern or poor compliance at the last follow-up visit.

mechanisms underlying the autoinflammatory picture are likely to exist. Gene expression analysis and functional studies performed in this cluster of patients may shed light on the molecular patterns set off by the R92Q mutation and guide the future therapeutic directions.

Acknowledgements

Carla Gaggiano and Donato Rigante equally contributed to this work.

Author contributions

C.G. and A.V. designed the study and performed statistical analysis with support of J.S.. C.G. carried out the main writing of the manuscript, with support from M.T. for literature selection. J.H.R., A.S., G.L., F.I., M.A.J., R.G., E.W.S., M.C., M.F., M.P., G.R., F.Z., A.F., V.S., M.T.H., O.A., L.P., A.F., C.F. and B.F. enrolled patients for the study, collected data and critically reviewed the manuscript for important intellectual content.

J.S., A.R. and S.G. critically reviewed the manuscript for important intellectual content. L.C. and D.R. supervised the study, contributed to the interpretation of results and to the final version of the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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