Efficacy and safety of canakinumab in cryopyrin-associated periodic syndromes: results from a Spanish cohort

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ABSTRACT

Objective. *Cryopyrin-associated periodic syndromes (CAPS) are dominantly-inherited autoinflammatory diseases. The uncontrolled IL-1β overproduction observed in these patients is the rational basis to treat them with anti-IL-1 drugs. The objective of this study was to evaluate the efficacy and safety of treatment with the long-lasting fully humanised anti-IL-1β monoclonal antibody canakinumab in a Spanish cohort of patients with CAPS.*

Methods. *Clinical and laboratory data of CAPS patients carrying a heterozygous germline NLRP3 mutation were obtained. The initial treatment scheme with canakinumab was 150 mg/8 weeks administered subcutaneously in adult patients and 2 mg/kg/8 weeks in paediatric patients.*

Results. *Eight unrelated patients were enrolled. Canakinumab was the first anti-IL-1 drug used in three of them; five were already receiving anakinra. The clinical response to the initial canakinumab scheme was positive in all patients, and was quickly observed in the first 24–72 hours. Four required increasing the frequency and/or dose of canakinumab. A limited or no efficacy in those symptoms related to consequence of the deforming arthropathy and neurosensorial deafness was observed. The adverse side effects were restricted to infectious complications in a small percentage of patients. The treatment was well tolerated by all patients, with no reactions at drug site injections.*

Conclusion. *Canakinumab caused fast and sustained remissions in most clinical and biochemical manifestations in all enrolled patients, with a limited efficacy in the structural lesions. Dose adjustments seem to be necessary for children and/or for patients with the most severe CAPS phenotypes. Treatment was well tolerated with a low incidence of adverse effects.*

Introduction

The term cryopyrin-associated periodic syndromes (CAPS) was first proposed in 2003 to group apparently different autoinflammatory diseases, but all caused by *NLRP3* mutations transmitted with an autosomal dominant inheritance pattern (1-2). A continuous disease severity spectrum has been proposed for CAPS, with familial cold autoinflammatory syndrome (FCAS; MIM#120100) at the less severe end, Muckle-Wells syndrome (MWS; MIM#191900) as an intermediate severity form, and chronic infantile neurological, cutaneous and articular (CINCA) syndrome (MIM#670115), also known as neonatal-onset multisystem inflammatory disease (NOMID), at the most severe end (2). All these different CAPS phenotypes share a group of clinical features (early onset of the disease, a generalised urticarial-like skin rash associated with a marked acute phase reaction as the main manifestations at the disease onset), while others are restricted to some phenotypes (AA-type amyloidosis in MWS, deforming arthropathy in CINCA-NOMID syndrome) (2-3).

The *NLRP3* gene encodes for cryopyrin, a protein that belongs to the family of Nod-like receptors (NLRs) (4). Cryopyrin is a component of the NLRP3-inflammasome, a multiprotein, cytosolic complex that generates the active forms of caspase-1 and certain inflammatory cytokines (IL-1β, IL-18, IL-33) (5). It has been shown that those *NLRP3* mutations associated with CAPS are 'gain-of-function' mutations that lead to a significant increase in the inflammasome activity as well as an unregulated overproduction of the aforementioned inflammatory cytokines (6-7). The specific overproduction of IL-1β in these syndromes constitutes the rationale to treat these patients with anti-IL-1 drugs (6-9). We herein describe the results of a multicentric, retrospective, observation-

al study on the efficacy and safety of the long-lasting, fully humanised anti-IL-1β monoclonal antibody canakinumab in a Spanish cohort of patients with CAPS.

Patients, material and methods

Patients

Both paediatric and adult Spanish patients with clinical manifestations consistent with those observed in CAPS syndromes and with a heterozygous, germline *NLRP3* mutation were enrolled in this study. It was conducted according to the Declaration of Helsinki, after obtaining informed consent from patients (or their parents/legal guardians) and approval of the ethics committee of Hospital Sant Joan de Deu.

Study design

This is a muticentric observational descriptive study to evaluate the efficacy and safety of canakinumab treatment in patients with CAPS. Clinical and laboratory variables were collected. All available data at the time of patient's enrolment were obtained by reviewing the patients' medical records, whereas those variables related to canakinumab treatment were collected in the control visits. Similarly, all the observed adverse events were recorded throughout the period of canakinumab treatment, regardless of a direct causal relationship could be established with the anti-IL-1 drug.

Results

Patients' clinical data

This study included 8 Spanish patients (7 males: 1 female), all of them carrying a heterozygous, germline *NLRP3* mutation (Table I). Only one patient (Pt 2) had familial history of the disease, with affected relatives in three consecutive generations (brother, mother and maternal grandfather). With regard to other concomitant diseases, only one patient (Pt 7) was remarkable for having ischaemic heart disease at age 38 years and cervical and lumbar disc hernias. The main clinical manifestations of the enrolled patients are shown in Table I. In addition to these, other different and occasional manifestations were detected such as lymphadenopathies (3 patients), splenomegaly (2 patients) and dentinogenesis imperfecta (1 patient). With regard to the CAPS phenotypes, it should be highlighted that all enrolled patients had moderate or severe forms (5 MWS patients, 2 CINCA-NOMID patients, and 1 patient with an overlap CINCA-NOMID/MWS), whereas none of them had a disease consistent with FCAS.

Efficacy of treatment with canakinumab

Previous to the study enrolment, three patients were receiving only symptomatic treatment (NSAIDs and corticosteroids), representing canakinumab the first anti-IL-1 drug administered in them. In contrast, the remaining five patients were already being treated with the anti-IL-1 drug anakinra (median treatment duration: 31 months; range: 18–55 months). The dose of anakinra that were receiving was 100 mg/24h in adult patients and 1 mg/kg/24h in paediatric patients. All patients experienced a fast clinical response to anakinra (median: 1 day; range: 1-2 days), which was considered as complete in two patients and partial in the remaining three as consequence of the appearance of acute outbreaks during the treatment period or by the persistence of skin lesions. The reasons to switch to canakinumab were a more convenient administration (4 patients) and the existence of severe local reactions to anakinra (1 patient). In all cases it was necessary to discontinue the anakinra treatment, followed by a wash-out period of a variable duration (median: 3 days; range: 2–14 days). Discontinuation of anakinra led to the appearance of an acute episode of the disease in all patients.

The initial canakinumab scheme was 150 mg administered subcutaneously every 8 weeks in adult patients, and 2 mg/kg/8 weeks in paediatric patients. With this scheme, a marked improvement of clinical symptoms was observed in all patients, which started in the first 24 hours of treatment. The first manifestations to disappear were the fever (8/8 patients) and the urticaria-like skin rash (7/7 patients), and subsequently the arthritis (4/4 patients), aseptic meningitis (3/4 patients) and papilloedema (1/2 patients). In contrast to these observations, canakinumab seemed to have a moderate effect on manifestations resulting from structural lesions. Thus, in the unique patient with AA-type amyloidosis, the treatment improved the kidney function and reduced the proteinuria, which could be considered as mild at analysis. With regard to the deforming arthropathy detected in two patients, the canakinumab treatment eliminated the inflammatory component associated to the arthropathy, but the skeletal lesion itself and its associated mechanical implications were unaffected. Finally, the neurosensorial deafness detected in three patients showed some improvement in only one of them and after 12 months of canakinumab treatment. Despite the marked clinical improvement detected with the initial canakinumab scheme, three patients (37.5%) required some modifications due to appearance of febrile episodes. In one patient the only change with regard to the initial scheme was the reduction of the administration interval to 4 weeks, whereas in the other two patients the changes included both the increase of the dose and the reduction of the administration interval (5 mg/kg/6 weeks in one patient and 8 mg/kg/4 weeks in the other) (Table II). No dose reduction and/or increase of the administration interval were performed in any patient.

With regard to the biochemical response, it was considered as complete in three patients (37.5%), in whom the inflammatory parameters were in the normal range during all the canakinumab treatment, and partial in four patients (50%), in whom a clear improvement was observed, but a sustained normalisation of the parameters was not achieved during all the treatment period. Interestingly, the group of patients with partial biochemical response included the two patients with the most severe CAPS phenotype (CINCA-NOMID syndrome) and those patients who required the greater adjustments to the initial treatment scheme (dose increase associated with shortening of the administration interval). The biochemical response could not be evaluated in one patient due the lack of data (Pt 8).

Adverse events

Table I. Clinical and genetic characteristics of patients.

Patient	Sex/ Age (years)	Onset (years)	Exanthema	Fever	Joint involvement		Neurological manifestations			Eye	Amylodosis involvement	Mutation Type AA	Diagnose NLRP3	Family history
					Arthritis	Artropathy	Meningitis	Papilledema	Hypoacusia					
1	M / 3.1	1.25	-	Yes	Yes	-	-	-	-	-	-	p.R170S	MWS	-
2	M / 67	1st decade	Yes	Yes	Yes	-	-	-	Yes	Conjunctivitis	Yes	p.R260W	MWS	Yes
3	M / 27	Newborn	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Uveitis Bilateral papilitis	-	p.D303N	CINCA-NOMID	-
4	F / 15	Newborn	Yes	Yes	-	Yes	Yes	Yes	-	-	-	p.G307V	CINCA-NOMID	-
5	M / 10.3	Newborn	Yes	Yes	-	-	Yes	-	-	-	-	p.T348M	MWS	-
6	M/ 2.4	Newborn	Yes	Yes	-	-	Yes	-	-	-	-	p.N400Y	CINCA-NOMID / MWS	-
7	M / 52	23	Yes	Yes	-	-	-	-	Yes	Conjunctivitis	-	p.R452G	MWS	-
8	M / 15	3	Yes	Yes	Yes	-	-	-	-	Conjunctivitis	-	p.S710C	MWS	-

M: male, F: female, -: absence, MWS: Muckle-Wells syndrome.

Table II. Clinical and analytical results of patients treated with canakinumab.

Patient	Duration (months)	Dose	Treatment response	Clinical manifestations							Laboratory				Flare	Adverse events
				Exanthema	Fever	Arthritis	Artropathy	Meningitis	Papilledema	Hypoacusia	ESR (mm/h)		CRP (mg/dL)			
											Basal	Treatment[4]	Basal	Treatment[4]		
1	11	5 mg/kg/6 w	Partial	-	Improve.[1]	Disapp.	-	-	-	-	78	24 ± 11	126	6,8 ± 67	No	No
2	16	150 mg/8 w	Complete	Disapp. (24h)	Disapp.	Disapp.	-	-	-	Improve.[3]	48	11	51	5,4 ± 0,9	No	No
3	16	150 mg/8 w	Partial	Disapp.	Disapp.	Disapp.	Persistence	Improve.[2]	Persistence	Progression	94	19 ± 13,9	149	16,3 ± 45	No	No
4	17	150 mg/8 w	Partial	Disapp.	Disapp.	-	Persistence	Disappe.	Disapp.	-	37	16 ± 1,4	61	0,38 ± 0,31	No	No
5	41	2 mg/kg/8 w	Complete	Disapp. (24h)	Disapp.	-	-	Disapp.	-	-	n.d.	n.d.	8,7	0,74 ± 8,8	No	Appendicitis
6	8	8 mg/kg/4 w	Partial	Disapp. (24h)	Improv.[1]	-	-	Disapp.	-	-	40	30,5 ± 19	6,3	4,2 ± 6,1	No	No
7	11	150 mg/4 w	Complete	Disapp. (24h)	Improv.[1]	-	-	-	-	Stabilisation	85	3 ± 5,2	0,3	0,3 ± 1,5	No	No
8	12	150 mg/8 w	Complete	Disappe. (24h)	Disapp.	Disapp.	-	-	-	-	5	4 ± 2,1	0,8	0,1 ± 0,07	No	No

-: absence; n.d.: not done, disapp.: disappearance, improve.: improvement
[1]Patients that required a modification of the initial canakinumab treatment scheme, [2]Ocasional neck pain, no other meningeal signs
[3]Hypoacusia improvement after 1 year treatment. [4]Median ± SD

Local reactions at the site of administration, with variable duration (1 week –1.5 months), were observed in three out of five (60%) patients who received anakinra, which did not require additional measures in two of them and that provoked the switch to canakinumab in the third. No infectious conditions were observed in any of the five patients treated with anakinra. In the 8 patients who received canakinumab, no local reactions were registered at the site of administration, and only one patient experienced mild upper respiratory infections in the winter season. Finally, it should be highlighted that one of the enrolled patients (Pt 5) suffered from an acute appendicitis during canakinumab treatment, which was subsequently complicated with an intra-abdominal abscess that was successfully resolved with abdominal surgery and antibiotic therapy.

Discussion

The uncontrolled overerproduction of IL-1β detected in patients with CAPS was the rational basis for starting treatment with anti-IL-1 drugs in these patients (6, 10-13). There are currently three different commercially available anti-IL-1 drugs to treat patients with CAPS named anakinra, canakinumab and rilonacept. These drugs have different mechanisms to block IL-1 and show subtle differences regarding efficacy, but remarkable differences regarding schemes of administration, adverse effects and immunogenicity. Canakinumab is a long-lasting, fully humanised monoclonal antibody that selectively blocks IL-1β (13). Its half-life is 28–30 days, which allows more confortable administration regimens than the other drugs (every 8 weeks for canakinumab in contrast to daily administration for anakinra or weekly for rilonacept).

In the present study a fast and marked improvement was observed in all patients for nearly all clinical symptoms since the first dose of canakinumab. The only manifestations for which this clear improvement was not observed were those due to structural lesions such as the deforming arthropathy or neurosensorial deafness, and to a lower degree AA-type amyloidosis. In 62% (5/8) of the enrolled patients the complete clinical response persisted over time with the initial treatment scheme, whereas 38% (3/8) required some modification, due to partial improvement, recurrence of fever episodes and/or skin rash. The disease control with canakinumab observed in our series was somewhat worse than those initially published, which reported a complete control with the first dose in all patients (13). The main difference between both studies is likely related to the CAPS phenotypes of the enrolled patients, as those patients from our cohort who required a change in the scheme of canakinumab administration were children with the most sever form of CAPS while those included in the first reported study suffered from MWS, the intermediate CAPS phenotype. We must notice that our results are similar to those published in two phase III study, which reported the need to increase the canakinumab dose and/or the frequency of administration in 24% and 68% of the enrolled patients, most of whom were children and/or patients with the most severe CAPS phenotypes (14, 15).

With regard to the biochemical response to canakinumab, it could not be properly evaluated in one patient because his biochemical parameters were normal at the start of treatment, and also remained normal during the treatment period. Although an unusual finding in CAPS, this patient had a clear mutation and clinical picture that improved completely with the treatment. In the remaining patients a significant reduction of these parameters until normal levels was observed. This response was considered complete and sustained in three patients, and partial in the remaining four patients, as oscillations of the biochemical parameters were detected throughout the treatment period. These oscillations were detected during the relapse of febrile episodes in three patients, who required a change in the initial treatment scheme, and probably related to the CAPS clinical phenotype in the fourth, because he was the most seriously ill patient in the group. Theoretically, the marked and persistent reduction of acute phase reactants observed during the treatment period should be associated with a reduction of the risk of AA-type amyloidosis, because the plasma level of the serum amyloid A protein is the main risk factor for the development of this life-threatening complication (16).

The safety and tolerance profiles of canakinumab in the enrolled patients were very good. The most common adverse effects of the different anti-IL-1 drugs are the local reactions at the site of drug injection and a somewhat higher incidence of upper respiratory infections. In a previous phase III study with 19 Japanese patients treated with caakinumab 2 patients had serious adverse events, which resolved with standard treatment, and 1 patient reported a mild injection-site reaction (14). In the present study, the incidence of respiratory infections can be considered low (12.5%), while none of the enrolled patients experienced local reactions at the site of drug injection, an adverse effect that was observed in 60% of patients of the same series who had been previously treated with anakinra. The marked difference observed in the incidence of this adverse event with anakinra and canakinumab in the same patients are probably related to the difference in the frequency of administration, which is daily for anakinra and every 8 weeks for canakinumab. Finally, we should highlight that an acute appendicitis subsiquently complicated with an intra-abdominal abscess was observed in a paediatric MWS patient during the treatment with canakinumab. Thus, given the frequency of acute appendicitis in the paediatric population, it is reasonable to consider the existence of a causal relationship between canakinumab and this complication. However, the appearance of intra-abdominal abscesses complicating an acute appendicitis is uncommon, and in this case we believe that anti-IL-1 drug may have played a role in its development. Both complications were recorded as serious adverse events during the treatment period with canakinumab, and were successfully treated according standard without requiring canakinumab discontinuation.

Despite the obvious limitations of this observational study, the data here shown demonstrate a marked, fast and

sustained efficacy of canakinumab in patients with CAPS. Those patients suffering from the most serious CAPS phenotypes probably will need changes from the initial scheme here described by means of increasing the drug dose and/or the frequency of administration. In our experience canakinumab had had a limited or no efficacy to control some clinical features consequence of structural lesions (deforming arthropathy, neurosensorial deafness), which are probably the result of the disease damage during several years. The marked and sustained reduction in the biochemical parameters observed with canakinumab theoretically should also reduce the risk of the appearance of AA-type amyloidosis. Finally, in spite of the obvious limitations of this observational study we consider it must be remarked the safety and tolerance profile of canakinumab.

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