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PHARMACOECONOMICS STUDY OF CANAKINUMAB IN PATIENTS WITH CRYOPYRIN-ASSOCIATED PERIODIC SYNDROMES (CAPS)

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Abstract: *In this study we conducted pharmacoeconomic assessment of the use of canakinumab in patients with cryopyrin-associated periodic syndromes (CAPS) versus the symptomatic treatment alone. Incidence of remission in the treatment group was selected as the efficacy endpoint, and superior efficacy of canakinumab was demonstrated in the treatment group as compared to the symptomatic treatment. Based on cost-effectiveness analysis, it was determined that canakinumab treatment required considerable expenses; however, due to the small number of patients the impact on overall budget will be insignificant. It should also be noted that the treatment with this medicinal product will help reduce the costs of out-patient and policlinic care, in-patient medical care, as well as administration-related and complications management costs.*

Key words: *cryopyrin-associated periodic syndromes (CAPS), canakinumab, glucocorticosteroids, amyloid disease, sensory deafness, uveitis, complications, auto-inflammatory syndromes, interleukine-1, C-reactive protein.*

Introduction

Cryopyrin-associated periodic syndromes (CAPS) is an auto-inflammatory disorder with autosomal dominant mode of inheritance characterized by recurrent episodes of systemic inflammation accompanied by fever, rash and joint pain. The incidence of CAPS is estimated to be 1:1,000,000. This syndrome is encompassing three phenotypes which for a long time were considered as different nosologic entities. The following conditions are distinguished in the CAPS:

– familial cold auto-inflammatory syndrome – FCAS;
– Muckle–Wells syndrome – MWS;
– chronic infantile onset neurologic cutaneous articular/neonatal onset multisystem inflammatory disease – CINCA/NOMID) [1,2, 3, 4, 5].

Patients with FCAS are characterized by mild course of the disease, whereas clinical picture of MWS and CINCA/NOMID is represented by more severe CAPS forms which are associated with the occurrence of such complications as sensory deafness, amyloid disease, and even vision loss in some cases [4]. No generally accepted standards of care and recommendations are available for the CAPS. Thus far, treatment of patients with CAPS has been performed with symptomatic treatment alone. However, the launch of a novel product Canakinumab (Ilaris®), targeting main pathogenesis pathways, has opened up new perspectives in the treatment of this population cohort. Canakinumab is a fully human monoclonal antibody with high affinity to interleukine-1b, being one of the key pro-inflammatory cytokines involved in the CAPS development mechanism [6]. Therefore, the choice of CAPS therapy method requires thorough analysis and must be reviewed in terms of clinical efficacy and cost-effectiveness of its use.

Study objective

Pharmacoeconomic assessment of the use of canakinumab in patients with diagnosed CAPS.

The following study tasks were determined in accordance with the study objective:

1. Efficacy analysis of the use of canakinumab and symptomatic treatment in patients with CAPS;
2. Analysis of costs required for the treatment of patients with CAPS;
3. Cost-effectiveness analysis;
4. Budget impact analysis on transition from symptomatic treatmen to canakinumab treatment.

Materials and methods

Efficacy analysis

We performed a literature review to extract results of clinical trials where the efficacy evaluation of treatment with canakinumab in patients with CAPS was determined as attainment of remission or complete clinical response. In this case remission was considered as the absence of the disease activity or presence of minimum activity in the opinion of the doctor, absence of skin rash, as well as normal blood plasma levels of C-reactive protein and SSA.

According to a double-blind, placebo-controlled efficacy and safety study of canakinumab in patients with CAPS, at Week 48 the percentage of patients attaining main remission criteria was 97 % [3]. No studies were performed to evaluate the efficacy of symptomatic treatment. For this reason, a survey among medical experts was conducted during this analysis to clarify the aforesaid criteria. For instance, Mrs. Svetlana Olegovna SALUGINA (V.A. Nasonova Scientific and Research Institute of Rheumatology, pediatric department) estimated the proportion of patients in remission at that specific study period for the patient group receiving symptomatic treatment to equal 12.5%.

Cost analysis

As no standards of care and recommendations are available for the CAPS, a survey was conducted among HCPs to determine the main costs. As a result, the following cost structure was identified for the treatment of patients with CAPS:

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– pharmacotherapy costs;
– administration-related costs;
– disease diagnostic costs;
– out-patient and policlinic treatment costs;
– in-patient treatment costs;
– adverse effects management costs;
– flare-up complications-related costs.

Pharmacotherapy costs

Canakinumab treatment costs were evaluated pursuant to the instruction for medical use. It was established that an average of 6.5 subcutaneous injections annually would be required to perform canakinumab therapy. It has to be noted that sharing of vials is commonly used in real clinical practice which reduces per patient costs. Furthermore, it was determined that in some cases the UK National Institute for Health and Clinical Excellence – NICE) provides recommendations to include sharing plans to evaluate administration-related costs for injectable dosage forms [7]. For which reason, an additional plan was included into the pattern accounting for sharing vials in 75 % of patients receiving canakinumab. Pharmacotherapy costs considering sharing vials in patients with CAPS equaled to 1 977 198 RUR.

In evaluating treatment costs in the comparator symptomatic treatment group, information obtained from surveying was used. It was determined that non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticosteroids (GCs) were used in the group of patients with milder form of CAPS. Treatment of patients with MWS is performed using NSAIDs, GCs, methotrexate (MT), and in some cases also tocilizumab, since NSAIDs, GCs, MT are used as therapy for patients with CINCA/NOMID. Drug prices were derived from the list of maximum sale prices, and the prices for drugs not included into the Vital and Essential Drugs (VED) list were found in the main distributors' pricelists. Based on expert opinion, pharmacotherapy costs were calculated for patients with CAPS considering frequency of indication, duration of use, as well as allocation of patients by clinical presentation. Thus, annual symptomatic treatment costs per patient with CAPS equaled to 48, 457 RUR.

Administration-related costs

Canakinumab and methotrexate therapy requires subcutaneous administration. Based on 'Time and motion' study findings for various dosage forms, it has been established that the median administration time for subcutaneous dosage forms was 12.6 min. This value was used to determine costs associated with the time of nurse's administration of canakinumab and MT [8]. Tocilizumab therapy requires intravenous administration of the drug over one-hour period, that is accompanied by additional costs related to nurse's work, intravenous infusion set, as well as to required amount of saline solution. Median administration-related costs for the canakinumab treatment group and symptomatic treatment group were determined as 547 RUR and 569 RUR, respectively.

Diagnostic, out-patient and policlinic and in-patient treatment costs

Disease diagnostic costs were calculated separately based on the survey findings and reached a total of 9, 769 RUR in the groups compared. Out-patient and policlinic and in-patient treatment costs were calculated following expert opinion considering frequency of indications, proportion of patients receiving the appropriate medical care, as well as the hospitalization rate and duration for each individual syndrome. Price information on medical services was taken from the tariffs of the Federal Compulsory Medical Insurance Fund. Median out-patient and polyclinic and in-patient treatment costs are presented in the Table 1.

Table 1. Annual diagnostic, out-patient and policlinic, and in-patient treatment costs

Cost item	Canakinumab treatment group, RUR	Symptomatic treatment group, RUR
Diagnostic costs	9 769	9 769
Out-patient and policlinic treatment costs	5 944	7 579
In-patient treatment costs	12 318	36 955

Complication management costs

The cost analysis included the costs related to treatment of the main complications occurring due to disease flare-up. Based on findings obtained from completed clinical studies of canakinumab, the decrease was observed in the disease complication rates to the extent of resolution in patients during the course of the trials. At the same time, such complication as hearing loss may not be evaluated to full extent due to limited period of the study. The present study has accommodated treatment costs for arthralgia, conjunctivitis, headache, myalgia, fever, depression, uveitis, as well as amyloid disease [3]. Complication management costs reached a total of 1 630 RUR for patients in the canakinumab group, and 14 301 RUR for the symptomatic treatment group.

Adverse effects management costs

The next step in the cost analysis was to determine the costs related to treatment of major adverse effects with very common, common and uncommon incidence rates (as per WHO classification) during the treatment with a relevant medicinal product. Core safety data were taken from instructions for medical use. Adverse effects (AEs) management costs were calculated based on appropriate standards of care and treatment recommendations. In this study calculation for adverse effects was performed for medicinal products requiring continuous use, specifically: canakinumab, prednisolone, methotrexate, and tocilizumab, with due account for the frequency of indications of the relevant medicinal product and the incidence rate of an emergent adverse effect during its use (Table 2)

Table 2. Adverse effects management costs for medicinal products used in patients with CAPS

Canakinumab, RUR	Prednisolone, RUR	Methotrexate, RUR	Tocilizumab, RUR
6 952	9 410	3 721	3 413

As the data in the Table 2 shows, the largest adverse effects management costs were attributed to prednisolone. To accommodate adverse effects management costs, the indication frequency of any appropriate medicinal product, the AE incidence rates, as well as treatment costs were considered. Thus, the adverse effects management costs for canakinumab group will reach a total of 6, 952 RUR, and 1, 431 RUR for the symptomatic treatment group.

The final step in the cost analysis was to sum up all the costs originated during a single year (Table 3).

Table 3. Cost analysis per patient per year

Cost item	Canakinumab treatment group, RUR	Symptomatic treatment group, RUR
Treatment costs	1 977 198	48 457
Administration-related costs	547	569
Diagnostic costs	9 769	9 769
Out-patient and policlinic treatment costs	5 944	7 579
In-patient treatment costs	12 318	36 955
Adverse effects management costs	6 952	1 431
Complication management costs	1 630	14 301
Subtotal:	2 014 358	119 060

As the data in the Table 3 shows, the total costs needed for treatment of patients in canakinumab group reach 2 014 358 RUR, and 119 060 RUR for treatment of patients in the symptomatic treatment group.

Cost-effectiveness analysis

Cost-effectiveness coefficient values were calculated by division of treatment costs over a 48-week period by efficacy criteria values for the appropriate patient group. As stated above, the remission attainment rate was selected as the efficacy criteria. The cost per 1 case of remission in canakinumab treatment was 3 050 659 RUR, whereas for the symptomatic treatment it was 1, 104, 665 RUR.

Budget impact analysis

This study evaluated the degree of budget impact for transition from a less efficacious symptomatic treatment to more effective canakinumab treatment during a single year of simulation of the entire population of patients with CAPS. According to expert opinion, there are about 30 patients with CAPS in the Russian Federation. Calculation of canakinumab pharmacotherapy costs included a plan of sharing vials in 75% of patients (Table 4).

Table 4. Budget impact analysis

Cost item	Canakinumab treatment group, RUR.	Symptomatic treatment group, RUR
Treatment costs	59 315 947	1 453 714
Administration-related costs	16 404	17 069
Diagnostic costs	293 063	293 063
Out-patient and polyclinic treatment costs	178 326	227 366
In-patient treatment costs	369 547	1 108 641
Adverse effects management costs	208 556	42 933
Complication management costs	48 908	444 702
Subtotal:	60 430 753	3 571 806

As the data in the Table 4 shows, the therapy with canakinumab requires a total of 60 430 753 RUR annually to treat 30 patients with CAPS, while a total of 3 571 806 is needed for symptomatic treatment. We then evaluated the difference in the monetary funds needed for the transition from symptomatic treatment to pathogenic treatment, that reached a total of 56 858 947 RUR. At the same time, a decrease was observed in direct medical costs by 1 168 909 RUR in transition from symptomatic treatment to canakinumab treatment at the expense of decreased costs for hospitalization, out-patient and polyclinic care, as well as treatment of complications.

Results

Attainment of remission reflecting clinical and laboratory signs of the disease was selected as the efficacy endpoint. In the canakinumab therapy remission is attained by 97 % of patients. Whereas for the symptomatic treatment this value is valid only for 12.5 % of patients.

Cost analysis per patient per year has shown that canakinumab treatment and symptomatic treatment require a total of 2 014 358 RUR and 119 060 RUR, respectively.

Based on the findings of the cost-effectiveness analysis, it has been determined that the costs per 1 case of remission for canakinumab treatment and symptomatic treatment alone reached a total of 3 050 659 RUR and 1, 104 665, respectively.

Budget impact analysis has demonstrated the difference in the required costs for transition from the supportive therapy to canakinumab treatment, which equaled 56 858 947 RUR.

Conclusions

In the course of this pharmacoeconomic study we have determined the costs for pharmacotherapy, administration, diagnostics of CAPS, out-patient and polyclinic, and in-patient treatment, adverse effects management, as well as management of CAPS-related complications. Based on the findings of the cost-effectiveness analysis, it has been determined that the costs per 1 case of remission for canakinumab were higher than for symptomatic treatment alone. Findings from the budget impact analysis have indicated the presence of budgetary expenditures for the transition from the symptomatic treatment to canakinumab treatment. At the same time, high efficacy of canakinumab treatment in patients with CAPS has resulted in the reduction of direct medical costs for out-patient and polyclinic care, hospitalizations, as well as costs for treatment of emergent complications as compared to the symptomatic treatment.

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