AMERICAN COLLEGE OF RHEUMATOLOGY/ ASSOCIATION OF RHEUMATOLOGY HEALTH PROFESSIONALS (ACR/ARHP) 2015 MEETING HIGHLIGHTS: NEW DATA ON CANAKINUMAB

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ABSTRACT

Interleukin (IL)-1 is a messenger for the regulation of inflammatory responses, but it can be harmful when in excess, such as in the inflammation observed in patients with autoinflammatory disease. Cryopyrin-associated periodic syndromes (CAPS) are a group of rare autoinflammatory diseases with an estimated population frequency ranging from 1–3 people per million.[1] These hereditary cytokine dysregulation syndromes encompass a spectrum of three cryopyrinopathies, including familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS), and neonatal-onset multisystemic inflammatory disease. In such genotypes, the *NLRP3* gene that encodes cryopyrin, an inflammation mediator involved in IL-1β processing, is mutated.

Canakinumab (CAN) is a humanised monoclonal antibody, which is administered subcutaneously and acts as an IL-β inhibitor drug, with a long plasma half-life (21–28 days) and an activity in the picomolar range. In the USA, CAN is indicated for the treatment of CAPS, including FCAS and MWS in adults and children. CAN was subsequently approved in 2013 for the treatment of active systemic juvenile idiopathic arthritis (SJIA) in patients aged ≥2.[2-4] The European Medicines Agency (EMA) approved CAN for the management of CAPS, gouty arthritis (GA), and SJIA in October 2009.[5]

New data on CAN use in CAPS is still emerging and CAN is also currently being evaluated in the treatment of other autoinflammatory diseases, including SJIA, as well as hereditary periodic fever syndromes and a range of other conditions, such as GA.[6-8] This article reviews the new preclinical and clinical evidence on CAN presented at the American College of Rheumatology/Association of Rheumatology Health Professionals (ACR/ARHP) meeting held in San Francisco, California, USA from 6th–11th November 2015.

Keywords: Canakinumab (CAN), cryopyrin-associated periodic syndromes (CAPS), cryopyrinopathies, familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS), neonatal-onset multisystemic inflammatory disease (NOMID), gouty arthritis (GA), systemic juvenile idiopathic arthritis (SJIA), interleukin (IL)-1β.

INTRODUCTION

Interleukin (IL)-1 is a messenger for the regulation of inflammatory responses but it can be harmful when in excess, such as in the inflammation observed in patients with autoinflammatory disease.[9,10] Canakinumab (CAN; Ilaris, Novartis Pharma, Hanover, New Jersey, USA) is a humanised monoclonal antibody that is administered subcutaneously (SC) and acts as an IL-1β inhibitor drug, with a long plasma half-life (21–28 days) and an activity in the picomolar range.[11,12]

The US Food and Drug Administration (FDA) first approved CAN as an orphan drug in June 2009,[2]

following the results of a double-blind, placebo-controlled, randomised withdrawal study of CAN in patients with cryopyrin-associated periodic syndromes (CAPS).[13,14] CAPS are a group of rare autoinflammatory diseases with an estimated population frequency ranging from 1–3 per million.[1]

These cytokine dysregulation hereditary syndromes encompass a spectrum of three cryopyrinopathies, including familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS) and neonatal-onset multisystemic inflammatory disease (NOMID). In such genotypes, the *NLRP3* gene that encodes cryopyrin, an inflammation mediator involved in IL-1β processing, is mutated.

In the USA, CAN is indicated for the treatment of CAPS, including FCAS and MWS in both adults and children. CAN was subsequently approved in 2013 for the treatment of active systemic juvenile idiopathic arthritis (SJIA) in patients aged ≥2.[2-4] The European Medicines Agency (EMA) approved CAN for the management of CAPS, gouty arthritis (GA), and SJIA in October 2009.[5]

While new data on CAN use in CAPS is still emerging, CAN is also currently being evaluated in the treatment of other autoinflammatory diseases, including SJIA, as well as hereditary periodic fever syndromes and a range of other conditions, such as GA.[6-8] At the American College of Rheumatology/Association of Rheumatology Health Professionals (ACR/ARHP) meeting held in San Francisco, California, USA from 6th–11th November 2015, new preclinical and clinical data from a total of 12 abstracts were presented on CAN.

NEW DATA PRESENTED AT ACR/ARHP 2015 ON CANAKINUMAB USE IN CRYOPYRIN-ASSOCIATED PERIODIC SYNDROMES

Results from an Open-Label, Multicentre, Phase III Trial

Efficacy and safety of canakinumab in patients with cryopyrin-associated periodic syndromes aged <24 months

At ACR/ARHP 2015, Brogan et al.[15] presented new data on Study D2307, an open-label, multicentre, Phase III trial evaluating the efficacy and safety of CAN in CAPS patients aged between 44 days and 4 years, thus providing new insight into the clinical use of CAN in patients aged <24 months.

The 17 enrolled patients received CAN at 2–12 mg/kg every 4 or 8 weeks, for 56 weeks. Six of the 17 patients were aged <24 months (44 days–5 months); 4 patients had MWS, 1 patient presented with FCAS, and 1 patient had NOMID. The latter received an initial dose of 4 mg/kg. Patients who did not achieve a complete response or experienced a flare before the next planned administration were eligible for dose up-titration with possible maintenance and step-wise up-titration regimens of 4, 6, or 8 mg/kg.

All patients achieved a clinical response, of which 16 (94.1%) had a complete response, defined by the Physician's Global Assessment (PGA) criteria as no or minimal disease activity and normal C-reactive protein (CRP) levels (<10 mg/L). Five (83.3%) out of 6 patients aged <24 months achieved a complete response. One patient, aged 1 years, did not reach a complete response and persistently had elevated CRP levels.

Four patients (2 MWS patients, 2 NOMID patients) subsequently relapsed but a complete response was regained with or without dose escalation in all four cases. Seven (41%) out of 16 patients required dose escalation to achieve and/or maintain their complete response. The proportion of complete responses without relapse was higher in the <24 months' age group (5/5; 88.9%) than the ≥24 months' group (7/11; 63.6%).

The safety profile of CAN was acceptable in younger patients and similar to that observed in older patients: the most common adverse events (AEs) were infections, mainly of the upper respiratory tract; though four patients experienced a serious AE (SAE), no SAE occurred more than once. No patient discontinued due to an AE.

Post-vaccination antibody titre data in cryopyrin-associated periodic syndrome patients aged between 28 days and 4 years treated with canakinumab

In patients with autoinflammatory diseases that are treated with immunosuppressive drugs, the increased risk of infections warrants vaccination against a range of bacteria or viruses.[16] CAN does not seem to affect protective antibody production after vaccination in healthy volunteers,[17] thus Brogan et al. aimed to evaluate such a setting in CAPS within the same Phase III trial.[18]

CAPS patients received CAN therapy as described above, alongside standard childhood inactivated

vaccines. Post-vaccination antibody titres were assessed during pre-dose assessment (Days 0–14), and at Days 28 and 57 after vaccination. Assessable patients were those who had a pre-dose and at least one post-dose antibody titre evaluation.

Seven out of 17 patients received one or more vaccinations against *Corynebacterium diphtheriae, Bordetella pertussis, Neisseria meningitidis, Clostridium tetani,* influenza types A and/or B, *Haemophilus influenzae B, Streptococcus pneumoniae,* or hepatitis B virus.

Eighteen out of 31 unique vaccination cases were assessable for a vaccination response, and all of those cases demonstrated protective levels at post-dose measurement. All of the 31 vaccination cases demonstrated protective level antibody titres at the last assessment, and no CAPS flares were reported.

These findings seem to confirm those data from Doran et al., as CAN appears to have no effect on antibody production against standard childhood inactivated vaccines.[16]

Safety and Efficacy of Canakinumab in Patients with cryopyrin-associated periodic syndromes: Interim Results from the Beta-Confident Registry

At ACR/ARHP 2015, Kümmerle-Deschner et al. presented the interim results from the β-Confident Registry, which is a multicentre, long-term, observational study managed by a steering committee of international experts. This registry comprises an enrolment period of 5 years, with a 1-year follow-up period to monitor the long-term safety (focussing on SAEs) and efficacy of CAN in CAPS.[19,20]

All observed and reported AEs and SAEs potentially related to CAN were recorded from the enrolment of the first patient (November 2009); interim data was reported until the current data cut-off date (September 2015). In the largest CAPS cohort documented in a registry to date, 288 patients from 39 sites across 13 countries were enrolled, with a mean patient exposure duration of 2.8 years.

CAN demonstrated a safety profile consistent with that observed in the clinical trial programme. CAN therapy was discontinued in 7.3% (n=21) of patients: five each due to AEs, poor efficacy, or patient preference; and six due to unknown reasons. The incidence rate (IR) per 100 patient-years (pyr; IR/100 pyr) for overall AEs was 112.5. Patients with FCAS had the lowest AE IR/100 pyr (60.9), compared with patients with MWS (107.2), and chronic infantile neurologic cutaneous and articular syndrome/NOMID (120.3).

The most common AEs were infections and infestations (IR/100 pyr: 39.6). Vertigo had an IR/100 pyr of 3.7 (n=19). One hundred and forty-eight SAEs were reported by 82 patients (IR/100 pyr: 16.7), the most common being infections (IR/100 pyr: 5.3). One death was reported in a 76-year-old MWS patient, as a result of metastatic rectal adenocarcinoma. Among the 21 patients who received pneumococcal vaccination, 68% (n=14) reported local post-injection site reactions, of which six were considered as serious.

Based on the PGA, CAN provided sustained efficacy over time in patients with CAPS for up to 5 years, as nearly half the patients had no disease activity and the majority of others experienced mild/moderate disease activity. Disease activity was mostly absent in *NLRP3* mutation-negative patients (n=14). No evidence of loss of effect was observed with time, but further analyses of this cohort are ongoing; enrolment is now complete and follow-up continued through December 2015.

NEW DATA PRESENTED AT ACR/ARHP 2015 ON CANAKINUMAB USE IN SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS

SJIA, previously referred to as Still's disease, is a debilitating form of arthritis associated with intermittent high and spiking fever, anaemia, leukocytosis, rash, elevated erythrocyte sedimentation rate, acute-phase reactants, and arthritis. As IL-1β plays a pivotal role in the pathogenesis of SJIA, the activity of CAN in the repression of several innate immunity and inflammation-related genes, including those involved in IL-1 signalling pathways for SJIA, has sparked a lot of interest.[21,22]

CAN was demonstrated as effective in two Phase III trials including patients with SJIA who exhibited articular and systemic features at treatment onset; subsequently CAN received FDA approval for use in SJIA treatment in May 2014.[23]

Efficacy and Safety of Canakinumab in Children with Systemic Juvenile Idiopathic Arthritis: Results from the Phase III Extension Study

Brunner et al.[24] presented the long-term safety and efficacy results of a Phase III extension study conducted in 123 CAN-naïve patients with SJIA, with or without fever at CAN initiation. Patients were aged 2–20 years at enrolment and received open-label CAN 4 mg/kg every 4 weeks. Seventy (57%) patients with, and 52 (42%) without SJIA-associated fever at study entry were available for analysis, for a median study duration of 96 weeks. Safety was assessed monthly.

At Week 2, 23.9% and 24.5% of patients with and without fever, respectively, had inactive disease. At Week 4, 73% and 81% of patients with and without fever, respectively, reached the SJIA adapted ACR30 response criteria (SJIA aACR30), defined as improvement of ≥30% in at least three of the six core ACR criteria for SJIA, worsening of >30% in no more than one of the criteria, and resolution of fever. At Week 12, the aACR rates increased to 89% and 92% in patients with and without fever, respectively. At Week 32 and beyond, 61.5% and 59.5% of patients had inactive disease, respectively.

Clinical remission on medication (i.e. 6 months of continuous clinical inactive disease) was achieved by 42.3% of patients in the overall group, of which 26.8% achieved for 12 consecutive months. Median Juvenile Arthritis Disease Activity Scores (JADAS) 27-CRP and 10-CRP were 6.0 (moderate disease activity) at Day 15 and 1.5 (low disease activity) at the last assessment, respectively.

The safety profile was acceptable and similar to the pivotal programme in SJIA patients with fever at enrolment. AEs were reported in 90% and 86.5% of patients with and without fever, respectively. SAEs were reported in 34.3% and 30.8% of patients with and without fever, respectively. Overall, eight events of macrophage activation syndrome (MAS) (patients with fever: n=6, patients without fever: n=2) were observed in both groups. No deaths or new safety signals were reported during the study. These results demonstrate the safety and efficacy of CAN in SJIA patients. CAN provided similar long-term efficacy, irrespective of the presence of systemic fever at treatment onset.

Efficacy of Canakinumab in Systemic Juvenile Idiopathic Arthritis Patients Previously Exposed to Biologics

Brunner et al.[25,26] also reported on an open-label extension study evaluating the use of CAN in 123 CAN-naïve SJIA patients previously exposed to anakinra (ANK) or tocilizumab (TCZ) versus biologic-naïve patients. CAN efficacy at 12 weeks has been previously demonstrated, regardless of biologic exposure.[27] In this study, 51 patients (42%) had previously received ANK and 31 (25%) TCZ, respectively, the main reason for treatment discontinuation being lack of efficacy; 44 patients were biologic-naïve.

At Day 29, SJIA aACR30/50 response rates were similar between ANK-naïve patients and those who discontinued ANK for lack of efficacy; the same applied for TCZ-experienced/naïve patients. At 12 months, SJIA aACR30 rates were slightly higher in ANK-naïve compared with those who discontinued ANK for lack of efficacy, but this was not the case for SJIA aACR50 rates. However, SJIA aACR50 response rates were higher in patients who discontinued TCZ due to lack of efficacy compared with TCZ-naïve patients.

There was a comparable initial and 12-month SJIA aACR response to CAN among biologic-experienced SJIA patients who switched from ANK or TCZ due to lack of efficacy, compared with biologic-naïve patients. These results demonstrate the consistent efficacy of CAN across different settings, including in prior biologic non-responders. A rapid response to CAN in the first month, maintained for up to 1 year, was observed. Extension studies are ongoing to provide long-term efficacy data across these different subgroups.

Macrophage Activation Syndrome in Systemic Juvenile Idiopathic Arthritis Patients Treated with Canakinumab: Results from a Phase III Trial Programme

MAS is a potentially fatal complication of SJIA that was reported as an AE in both CAN and placebo group patients from Phase III trials.[23] Thus, an independent expert MAS Adjudication Committee (MASAC) aimed to identify and adjudicate potential events. Grom et al.[28] reported the MASAC findings in CAN-naïve SJIA patients from the Phase III trial programme at ACR 2015.[26]

Potential MAS events were identified by periodic searches of the clinical study databases. MAS

events were then adjudicated, blinded to treatment as either probable, possible, or unlikely MAS, or labelled to highlight that there was insufficient information.[29] The MASAC identified 72 potential cases: 21 events in 19 patients were adjudicated as 'Probable MAS' (CAN: n=19; placebo: n=2), and 10 events in 9 patients as 'Possible MAS'.

The delay between the first injection of CAN and MAS onset ranged between 3–1,359 days (median: 531 days). The rate for MASAC-adjudicated 'Probable MAS' was 2.8/100 pyr and 7.7/100 pyr for the CAN and placebo groups, respectively, with no statistically significant difference (-4.9; 95% confidence interval [CI]: -15.6–5.9). Three patients (CAN: n=2; placebo: n=1) died due to complications of MAS; full recovery was reported in the remaining patients. These findings demonstrate that CAN does not appear to have an effect on the occurrence of MAS.

NEW DATA PRESENTED AT ACR/ARHP 2015 ON CANAKINUMAB USE IN HEREDITARY PERIODIC FEVER SYNDROMES

Hyperimmunoglobulinaemia D with Periodic Fever Syndrome

Hyperimmunoglobulinaemia D with periodic fever syndrome (HIDS) is a recessively inherited periodic fever syndrome disorder with episodes of high fever, abdominal distress, joint pain, and skin rashes.[30] Previous reports have suggested IL-1 inhibition as a potential therapy in HIDS.[8,31]

Open-label single treatment arm study: study d2402 - long-term efficacy and safety of canakinumab in active hyperimmunoglobulinaemia D with periodic fever syndrome

Arostegui et al.[32] presented the final results of a 36-month, open-label, single treatment arm study assessing the efficacy and safety of CAN in patients with active HIDS and biallelic mevalonate kinase mutations. The study comprised a 6-month treatment period (6mo-TP; 4 mg/kg every 6 weeks, max 300 mg delivered SC with one permissible dose up-titration to 6 mg/kg [max 450 mg] if a flare occurred in the first 6 weeks), an up-to 6-month follow-up period (6mo-FP), and a 24-month long-term treatment period (24mo-LTTP; same CAN dose administered at the last visit of the 6mo-TP).[33]

Eight out of nine patients completed all periods of the study. CAN demonstrated rapid disease control; the median number of flares decreased consistently during the study, from 5 (3–12) prior to therapy to 0 (0–2) during the 6mo-TP, and persisted (0–3) until the end of the study. Median time-to-flare after the last dose of CAN during the follow-up period was 110 days (range: 62–196 days).

During the 24mo-LTTP, median flare duration was 3.5 days in the first year and 8.5 days in the second. Improvements from baseline were observed on flare severity, as well as normalisation of plasmatic inflammatory markers (CRP and serum amyloid A [SAA]). No unexpected safety findings were observed through the study, and the safety profile of CAN was consistent with that reported in other studies.

Tumour Necrosis Factor Receptor-Associated Periodic Syndrome

Long-term efficacy and safety of canakinumab in patients with active recurrent or chronic tumour necrosis factor receptor-associated periodic syndrome: STUDY D2203

Tumour necrosis factor receptor-associated periodic syndrome (TRAPS) is a rare, hereditary periodic fever syndrome characterised by recurrent attacks of fever associated with rash, musculoskeletal and abdominal pain, conjunctivitis, and periorbital oedema.[34]

In an open-label, single treatment arm study with a 4-month treatment period, a 5-month follow-up period (treatment withdrawal), and a 24-month long-term treatment period, 20 patients with active TRAPS received monthly CAN 150 mg (2 mg/kg for patient ≤40 kg) SC.[35] Ninety per cent of patients completed the study. On Day 15, 95% (95% CI: 75.1–99.99) of patients achieved a complete or almost complete response, while 20 (100%) and 12 (60%) patients had clinical and serological remission, respectively. CRP and SAA levels were highest at baseline and decreased rapidly with treatment, remaining normal during the course of the study. At the end of the 4-month treatment period and the 24mo-LTTP, all patients had absent (95% and 84.2%, respectively) or minimal (5% and 10.5%, respectively) disease activity (versus baseline: 65% of mild, 30% of moderate, and 5% of severe disease activities). No new safety signals were reported during this long-term study, and the safety profile of CAN was consistent with those reported in other studies.

NEW DATA PRESENTED AT ACR/ARHP 2015 ON CANAKINUMAB USE IN ADULT ONSET STILL'S DISEASE

Adult-onset Still's disease (AOSD) is a rare autoinflammatory disorder and the analogous systemic clinical features of SJIA suggest that both disorders are part of the same disease continuum, only with different ages of onset.[36] Since IL-1β is emerging as a master mediator of AOSD, CAN use in this disease is beginning to be investigated.[37,38]

Preclinical Data: Gene Expression Analysis of Adult-Onset Still's Disease and Systemic Juvenile Idiopathic Arthritis Suggest a Single-Disease Continuum

Nirmala et al.[39,40] conducted a gene expression analysis on the genes that respond to CAN treatment in SJIA compared with patients with active AOSD and healthy subjects. Whole blood samples from 17 active AOSD patients and 19 healthy controls were collected; total RNA was subsequently isolated and gene expression profiles were performed using the Affymetrix U133 Plus 2.0 Array.

Genes that were downregulated in patients with SJIA following CAN treatment were inversely dysregulated in patients with active AOSD, relative to healthy subjects; this pattern correlated with neutrophil counts. These findings support the concept of a Still's disease continuum with both disorders, warranting further evaluation of anti-IL-1β therapies in AOSD patients.

NEW DATA PRESENTED AT ACR/ARHP 2015 ON CANAKINUMAB USE IN GOUTY ARTHRITIS

Patients with GA can suffer from acute flares characterised by pain and inflammation, for which nonsteroidal anti-inflammatory drugs and colchicine are currently the established management options. Additional effective and alternative therapies are needed however, due to contraindications, intolerance, or ineffectiveness.[41]

Extension Studies from Two Phase III, Multicentre, Double-Blind, Randomised Trials: STUDY H2357E3 - A 3-Year Follow-up Study of Canakinumab in Frequently Flaring Gouty Arthritis Patients, Contraindicated, Intolerant, or Unresponsive to Nonsteroidal Anti-Inflammatory Drugs and/or Colchicine

The 36-month safety results of the extension studies from two Phase III, multicentre, double-blind, randomised (CAN 150 mg SC and intramuscular triamcinolone acetonide [TA] 40 mg) trials (β-RELIEVED and β-RELIEVED-II) were presented.[42] 24-week results had been previously published.[43]

Of the 456 randomised patients from the core studies, 122 completed both open-label treatment phases.

The CAN safety profile was consistent with that observed in previous studies. Over 3 years, the exposure-adjusted incidence of AEs and SAEs in the CAN group was lower (264.6 and 17.3/100 pyr, respectively) than in the TA group (308.8 and 17.7/100 pyr, respectively). Retreatment with CAN did not increase the incidence of AEs or SAEs.

Over the 3-year study period, the mean 'on demand' number of doses observed per patient was 2.68. Efficacy of CAN was demonstrated via stable pain intensity levels and PGA response scores. Mean annual flare rates were lower in the CAN group (1.1) versus the TA Group (2.5).

Canakinumab Liquid Formulation in Acute Gouty Arthritis Patients: Long-Term Safety and Efficacy Results from a 36-Week Extension Study

The evaluation of the safety profile of emerging therapies for GA is crucial, since chronic kidney disease limits the treatment options for these patients. A 12-week, multicentre, double-blind, active controlled study was conducted to evaluate CAN liquid formulation in a pre-filled syringe (CAN-PFS) versus TA and secondarily the lyophilised form (CAN-LYO).[41,44] At ACR/ARHP 2015, Sunkureddi et al.[45] presented the 48-week cumulative safety and efficacy results following a 36-week open-label extension from the core study.

All patients entering received CAN-PFS 150 mg SC on demand upon new GA flare, irrespective of the assigned treatment during randomisation (CAN-PFS, CAN-LYO, or TA 40 mg). One hundred and ninety-eight patients out of 397 (50%) completed the extension study. Baseline characteristics were comparable between the treatment groups.

The safety profiles were consistent with those observed in previous studies. Over 48 weeks, the exposure-adjusted incidence of AEs and SAEs were lower for both CAN-PFS (254.9/100 pyr) and CAN-LYO (224.8/100 pyr) groups compared

with the TA (362.7/100 pyr) group. The exposure-adjusted incidence of SAEs was 14.7/100, 16.1/100, and 15.5/100 pyr, respectively, with infections and infestations being the most frequently reported. One death (cardiac failure), not suspected to be related to the study drug, was reported in a patient who was randomised to CAN-PFS but not re-treated during this period.

CAN-PFS significantly delayed time to first new flare compared with TA, with a relative risk reduction of 55% (hazard ratio [HR]: 0.45; 95% CI: 0.32–0.64; p<0.0001). Mean number of new GA flares was lower in both CAN-LYO (0.50) and CAN-PFS (0.76) groups than the TA group (0.96). Patients in the CAN-PFS group showed a 56% reduction in the number of new flares compared with the TA group (flare rate ratio: 0.44; 95% CI: 0.32–0.61; p<0.0001).

CONCLUSIONS

While two other drugs are approved for CAPS management, namely rilonacept, a recombinant soluble IL-1 receptor, and anakinra, a recombinant IL-1 receptor antagonist, CAN is the only agent targeting IL-1β selectively, thus possibly providing new strategies by addressing IL-1β-related inflammatory disorders with an improved safety profile.

Undoubtedly, additional evidence from both clinical trials and real-world registries or studies will help refine treatment pathways for the range of disorders for which IL-1β is involved, but CAN is a promising agent that could bring added value for clinicians in the treatment armamentarium of several diseases. In addition to CAN, two other anti-IL-1β antibodies, gevokizumab and LY2189102, are currently being evaluated in clinical trials.[46]

Click below to view the following videos:

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- **Treatment strategies for tumour necrosis factor receptor-associated periodic syndrome (TRAPS)**
- **Canakinumab in the treatment of tumour necrosis factor receptor-associated periodic syndrome (TRAPS)**
- **Pathophysiology and treatment of hyperimmunoglobulinaemia D with periodic fever syndrome (HIDS)**
- **Canakinumab in the treatment active hyperimmunoglobulinaemia D with periodic fever syndrome (HIDS)**

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