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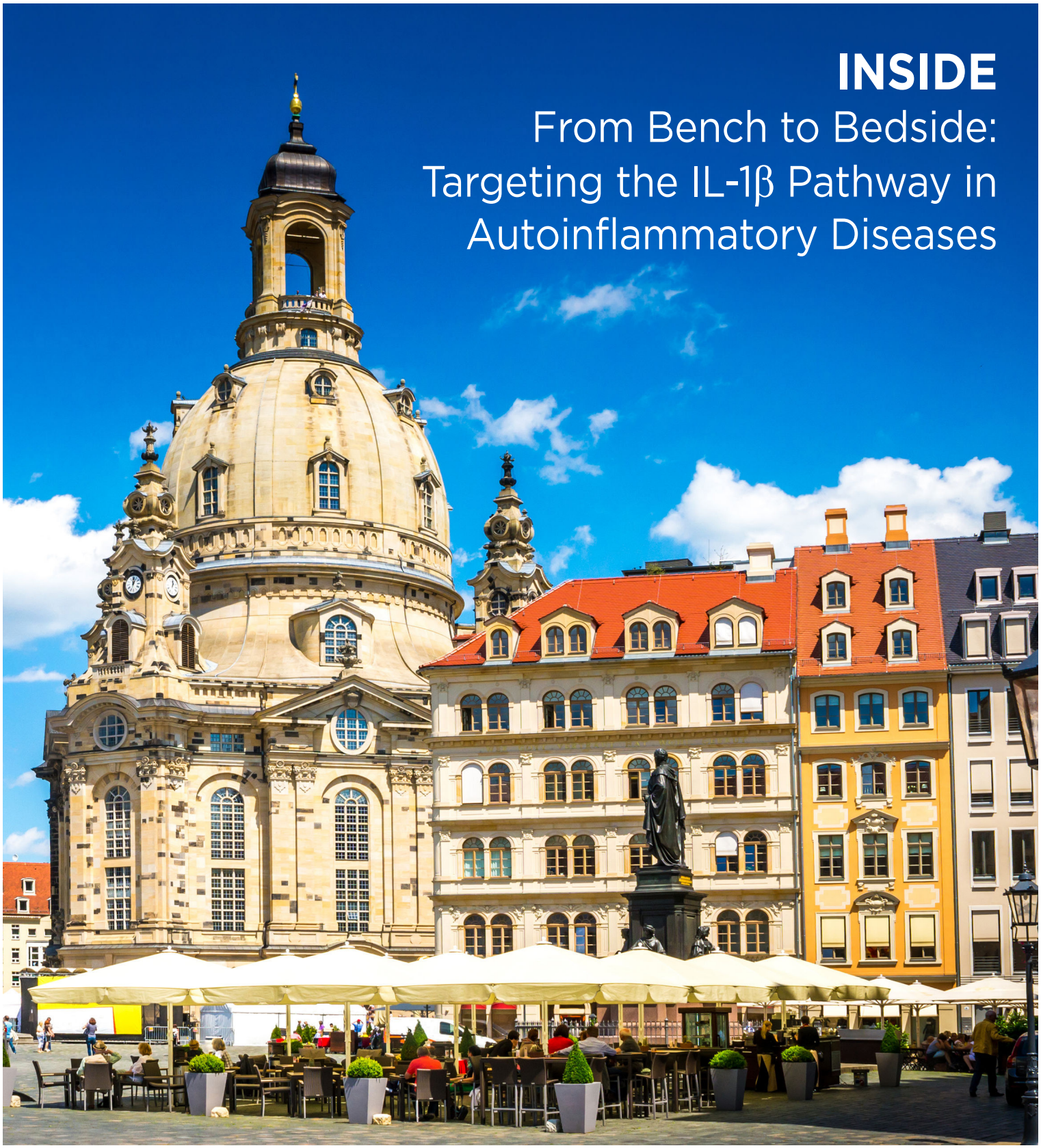

INSIDE

From Bench to Bedside: Targeting the IL-1β Pathway in Autoinflammatory Diseases

FROM BENCH TO BEDSIDE: TARGETING THE IL-1β PATHWAY IN AUTOINFLAMMATORY DISEASES

This symposium took place on 1st October 2015 as part of ISSAID 2015: the International Society of Systemic Auto-inflammatory Diseases' 8th International Congress of Familial Mediterranean Fever and Systemic Auto-inflammatory Diseases in Dresden, Germany

Chairperson

Gerd Horneff[1]

Speakers

Angelo Ravelli,[2] Jasmin B Kümmerle-Deschner,[3] Fabrizio De Benedetti[4]

1. Asklepios Clinic, Sankt Augustin, Germany

2. University of Genoa, Istituto Giannina Gaslini, Genoa, Italy

3. Division of Paediatric Rheumatology, University Children's Hospital Tübingen, Tübingen, Germany

4. Division of Rheumatology, IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy

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MEETING SUMMARY

Prof Gerd Horneff opened the symposium with a summary of the recent advances in the understanding of the role of interleukin (IL)-1β in the pathogenesis of autoinflammatory (AI) diseases. Prof Angelo Ravelli then discussed the concept of 'treat-to-target' in systemic juvenile idiopathic arthritis (SJIA) and the various tools that can be used for monitoring treatment response. Dr Jasmin B Kümmerle-Deschner followed with an overview of the efficacy and safety data from the β-Confident Registry of patients with cryopyrin-associated periodic syndromes (CAPS) receiving treatment with canakinumab. Prof Fabrizio De Benedetti concluded with an overview of the up-and-coming data in the field of AI diseases. The objectives of the symposium were to summarise new insights in the pathogenesis of AI diseases including the role of IL-1β; to evaluate the use of anti-IL-1β and other treatment options for AI diseases; to describe the treat-to-target concept and recognise the potential of a tight disease control strategy in patients with SJIA; to integrate new knowledge on the long-term use of canakinumab in patients with CAPS based on the latest β-Confident Registry data; and to discuss management strategies in patients with AI diseases.

Recent Advances in Understanding the Role of IL-1β in the Pathogenesis of Autoinflammatory Diseases

Professor Gerd Horneff

Prof Horneff began by describing the case of a 5-year-old girl who presented with urticaria and elevated C-reactive protein (CRP) levels at 5 months of age. At 4 years of age she displayed transient synovitis, knee joint pain, fever, leukocytosis, and an elevated erythrocyte sedimentation rate (ESR) and CRP level. Two of her maternal cousins were deaf. At age 5 years she presented with swelling of the right ankle, leukocytosis, elevated CRP and ESR, and fever. A diagnosis of osteomyelitis was apparently confirmed by technetium scintigraphy, and the fever disappeared following treatment with clindamycin. However, CRP remained elevated after 4 weeks, and 3 months later she displayed fever and urticaria. The patient presented at the Paediatric Rheumatology Department, University Children's Hospital, Tübingen, Germany, where a diagnosis of CAPS was suspected due to the family history of hearing loss. Genetic testing was positive, audiometry demonstrated high-tone hearing loss, and ophthalmology identified uveitis; glaucoma developed later.

CAPS is characterised by fever, exanthema (urticaria), malaise/weakness, osteitis/arthritis, aseptic meningitis, uveitis, neurosensory hearing loss, and amyloidosis.[1] It is caused by mutations in the *NLRP3* gene that encodes the cryopyrin protein, which forms the inflammasome together with the pyrin domain of an apoptosis-associated speck-like protein containing a caspase activation and recruitment domain (ASC).[2] When activated by danger signals, for example, signals from cytokines, cryopyrin dimerises with a ASC and procaspase to form the inflammasome, which triggers caspase-1 to activate IL-1 and IL-18, which are then secreted in an autocrine fashion, enhancing the inflammatory response.[3]

Canakinumab is a fully human, selective, anti-IL-1β, monoclonal antibody[4-6] with no binding activity towards IL-1β or IL-1 receptor antagonists. Canakinumab prevents IL-1β from binding with its receptor, thereby inhibiting its proinflammatory signalling. It has a long mean terminal half-life of 26 days[5] and has demonstrated efficacy and a favourable safety profile in patients with CAPS.[6] The patient began treatment with canakinumab every 2 months following the episode of fever and ankle pain, and her CRP and serum amyloid A (AA) levels reduced. Some symptomatic recurrences occurred, and the dose was adjusted accordingly. The patient is currently feeling well; the hearing loss disappeared 2 months after starting treatment.

A three-part, 48-week, double-bind, placebo-controlled, randomised, withdrawal study with canakinumab was conducted in 35 patients with CAPS (aged 4–75 years).[6] In part 1, patients received canakinumab 2–4 mg/kg (150 mg) open-label for 8 weeks to identify responders; almost all patients (97%) responded by Day 29 and entered part 2. Part 2 was a double-blind, placebo-controlled period to assess efficacy; patients randomised to canakinumab remained in remission, while patients randomised to placebo experienced disease flares (Figure 1). There are several clinical classifications for AI disease as given in Table 1.

A proof-of-concept Phase II study was conducted in patients with familial Mediterranean fever (FMF). In the study, patients received 2 mg/kg (max 150 mg) canakinumab, given three times every 4 weeks, with the first dose given during an attack.[9] Six of the seven patients had a ≥50% reduction in their FMF attack rate and the median attack rate was reduced by 89% (0.3–2.7 attacks/28 days) with only two patients requiring dose up-titration. A marked improvement was observed in the condition of all patients from baseline to Month 3.

In addition to its association with genetic diseases, the *NLRP3* inflammasome is involved in many chronic inflammatory conditions, including SJIA. The first part of a complex, double-blind, placebo-controlled clinical trial showed canakinumab to be efficacious in SJIA. Patients receiving canakinumab showed a response as early as Day 15 which lasted to Day 29.[10] In the second part of the study, patients received open-label canakinumab with reduced steroid dosage. When they were stable and corticosteroid-free they entered a second double-blind treatment phase. At the end of the open-label phase many patients showed a response as per the juvenile idiopathic arthritis American College of Rheumatology (JIA ACR) criteria. When they entered the second double-blind treatment phase, the number of disease flares was higher in the placebo group.

AI diseases may also be classified according to the biological mediator: IL-1-mediated, interferon-mediated (e.g. STING-associated vasculopathy

with onset in infancy [SAVI]), those caused by increased nuclear factor kappa B, those caused by persistent macrophage activation, and those with as yet uncharacterised pivotal proinflammatory mediators.[11] The case of an Italian boy, the second child of a non-consanguinous family, who presented with fever and skin eruptions associated with exposure to cold, was described. He displayed necrosis of the finger tips and tongue. There was pulmonary involvement and the disease was refractory to steroids, immunosuppressants, tumour necrosis factors, IL-6, and IL-1 inhibitors. Genetic testing revealed a diagnosis of SAVI,[12] an autosomal dominant inherited condition resulting in activation of STING (an adaptor protein in the cytosolic DNA-sensing pathway) and secretion of IL-1. Another case was described of a male patient who remained undiagnosed for 17 years.

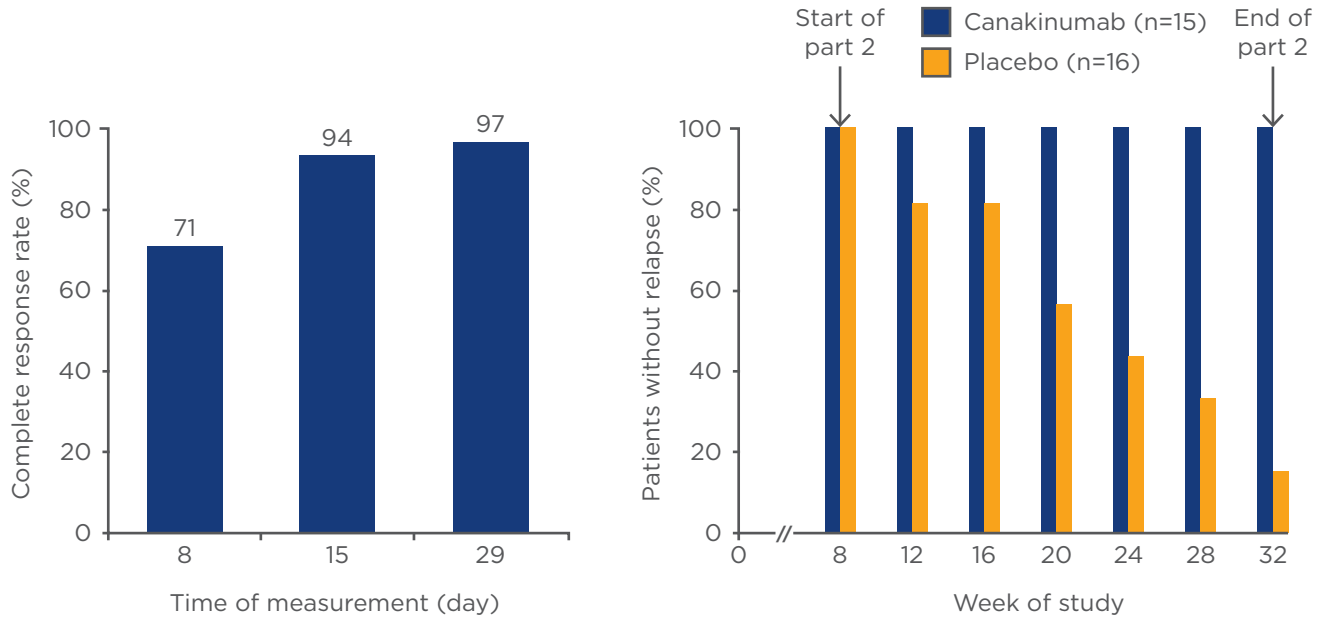

Figure 1: Use of canakinumab in patients with cryopyrin-associated periodic sydromes.[6]

Table 1: Classification of AI diseases.[7,8]

Classification	Examples
'Classic' periodic fever diseases	• Familial mediterranean fever* • Cryopyrin-associated periodic syndromes/familial cold autoinflammatory syndrome 1* • Tumour necrosis factor receptor-associated periodic syndrome* • Hyperimmunoglobulin D syndrome/mevalonate kinase deficiency*
Diseases with pyogenic lesions of the skin and bone	• Deficiency of IL-1 receptor antagonist* • Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome* • Majeed syndrome
Diseases associated with granulomatous lesions	• Blau syndrome • Familial Crohn's disease
Diseases associated with psoriasis	• Deficiency of IL-36 receptor antagonist
Diseases associated with defects in the immunoproteasome	• Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome (joint contractures, muscular atrophy, microcytic anaemia, panniculitis-induced lipodystrophy syndrome, and Nakajo-Nishimura syndrome)
Others	• Histiocytosis-lymphadenopathy plus syndrome • Polyarteritis nodosa, childhood-onset/deficiency of adenosine deaminase-2

*Genetic AI disorders linked to the *NLRP3* inflammasome.
IL: interleukin.

He had recurrent fever episodes beginning in infancy, short stature, flat and nodular skin eruptions (panniculitis) resulting in lipodystrophy, arthritis and myositis, chronic anaemia, and elevated acute phasereactants. Several treatments were prescribed, all of which failed to address the symptoms including corticosteroids, cyclosporine A, and tocilizumab. Some success was achieved with thalidomide and growth hormone. At the age of 17 years, genetic testing revealed chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome,[13] which is caused by mutations of the proteasome leading to increased Type I interferon activity.[8] In conclusion, although the diseases described are rare, physicians should still be vigilant for their presentation.

Future Perspectives in Systemic Juvenile Idiopathic Arthritis Management: Can we Treat-To-Target in Paediatric Patients?

Professor Angelo Ravelli

In recent years there have been significant advances in the management of JIA including the introduction of methotrexate, more widespread use of intra-articular corticosteroid injections, and the availability of new biologic medications. Remission has therefore become an attainable goal for most patients. Achieving an inactive disease state at least once in the first 5 years of the disease has been shown to improve long-term outcomes in terms of physical function and clinical and structural joint damage,[14] and is therefore an important treatment goal.

A biphasic model of SJIA has been proposed within which the innate immune system, particularly IL-1, plays a major role.[15] Based on this model, it has been proposed that the early suppression of IL-1 may be helpful in controlling extra-articular disease manifestations such as fever, and may also help to prevent disease progression to chronic SJIA. A prospective pilot study showed that early administration of IL-1R antagonists in steroid-naïve patients with new-onset SJIA led to a high rate of therapeutic response (>80% at 3 months) that was maintained over time, even after treatment with the IL-R antagonist was stopped.[16]

The 'treat-to-target' strategy involves aiming for the best possible control through regular measurements of disease activity and treatment intensification according to quantitative clinical indices.[17] An initial target is set, i.e. a state of inactive disease (or minimally active disease in very severe patients), the level of disease activity is assessed every 1–3 months, and the treatment level is maintained or intensified accordingly. Over time, if the target is maintained, treatment may be discontinued. The TIght COntrol for Rheumatoid Arthritis (TICORA) study found that patients treated using the treat-to-target method had lower disease activity when measured with the Disease Activity Score, compared with patients who were given routine treatment 20 months after treatment initiation.[18] There is a growing interest in application of the treat-to-target approach for JIA.[19]

Several disease activity measurements are available. The Juvenile Arthritis Disease Activity Score (JADAS) includes four measures of disease activity of which there are three different versions (JADAS 71, 27, or 10) depending on the type of joint count used.[20,21] Each JADAS measures Physician's Global Assessment score (visual analogue scale [cm]: 0–10), parent's/patient's global assessment (visual analogue score [cm]: 0–10), active joint count (complete: 0–71; reduced: 0–27 or 0–10), and acute phase reactant (ESR or CRP normalised: 0–10). A shorter version, which does not include the acute phase reactant, (clinical JADAS [cJADAS]), has been shown to be more feasible in clinical practice with similar performance to the original JADAS tool.

The identification of cut-off points in the JADAS/cJADAS that relate to levels of disease activity has been a major development,[22-24] and may be particularly useful for clinical decision-making in the treat-to-target approach. Plotting the JADAS over time permits easy analysis of the peaks and troughs of disease activity and response to treatment.[25] This is especially useful in patients with long-term illnesses such as chronic JIA. However, despite the improvements to the JADAS, there is no specific version for SJIA. A proposed systemic JADAS (sJADAS) is in development; it includes a fifth item, the systemic manifestation score, which incorporates fever, rash, generalised lymphadenopathy, hepatomegaly and/or splenomegaly, serositis, anaemia, and platelet count.

The JADAS may also be used to assess the results of therapeutic intervention in the clinical trial setting. Data from the Phase III studies of canakinumab show improvements in the median

JADAS27-CRP score over time, particularly in the first 15 days following treatment.[26] The majority of patients maintained or improved their response to canakinumab (based on JADAS27-CRP cut-offs for inactive disease, low disease activity, moderate disease activity, and high disease activity) from Day 15 to Day 85.[27]

It has been suggested that immunological targets or imaging-defined targets may be more useful for assessing disease activity than clinical targets. Myeloid-related protein (MRP) 8/14 has been shown to be highly predictive of disease flares after withdrawal of methotrexate following achievement of remission ($p<0.001$). MRP8/14 levels were higher in patients with an early disease flare (within 3 months of treatment discontinuation) compared with patients who had a late flare (within 6 months).[28] Some patients with JIA in clinical remission were found to have evidence of ongoing activity in the joints on ultrasound[29] or magnetic resonance imaging.[30] In the adult rheumatology field, it was found that patients with subclinical synovitis had a greater risk of developing structural abnormalities or functional limitation than those who did not.[31,32] However, the implications of these findings for JIA are unclear. In a 2-year study that evaluated ultrasound features in children with inactive disease,[33] a comparison of the baseline ultrasound features after follow-up found no differences in synovial hyperplasia, joint effusion, and tenosynovitis between children with sustained remission (inactive disease for up to 2 years) and those with synovitis flares. However, significantly higher power Doppler signals (a marker of active synovitis) were seen in patients with sustained remission,[33] therefore it is not yet known if ultrasound can predict the risk of flares in JIA.

Long-Term Treatment with Canakinumab in CAPS Patients: Insights from the β-Confident Registry

Doctor Jasmin B Kümmerle-Deschner

The β-Confident Registry comprises patients with CAPS who are treated with canakinumab. CAPS is a spectrum of disease, ranging from the mild familial cold autoinflammatory syndrome to Muckle–Wells syndrome (MWS) and severe neonatal-onset multisystem inflammatory disease/chronic infantile neurological, cutaneous, articular syndrome (NOMID/CINCA). Although initially thought to be separate diseases, these were amalgamated under the term CAPS following the discovery of missense mutations in *NLRP3*.[34] To date >176 *NLRP3* mutations have been described;[35-37] however, genetic mutations can be found in only 50–70% of patients with MWS and NOMID.[34] Mutations in *NLRP3* lead to dysregulation of IL-1β production due to activation of the inflammasome,[38] and produce a range of symptoms, including fever, headache, arthralgia, arthritis, myalgia, abdominal pain, urticaria, conjunctivitis, and severe fatigue. If untreated, long-term sequelae of MWS and NOMID/CINCA include sensorineural hearing loss, visual loss, cognitive impairment, damage to the central nervous system, growth retardation, bone and joint deformities, AA amyloidosis, and renal failure.

Dr Jasmin B Kümmerle-Deschner described the case of a 12-year-old boy who had presented since birth with an urticaria-like rash and displayed fever, enlarged lymph nodes, headache, conjunctivitis, hepatosplenomegaly, arthralgia, myalgia, and arthritis. At presentation he had severe hearing loss, cognitive retardation, growth delay, skeletal deformities, increased inflammatory parameters, including elevated CRP, ESR, and serum AA, leukocytosis, and anaemia. Genetic testing revealed an *NLRP3* mutation. After only 3 days of treatment with canakinumab, the patient was described by his parents as a 'different child', displaying no CAPS-related symptoms. After 4 months, almost all of the inflammatory markers normalised and he is now on a stable dose of 300 mg canakinumab every 4 weeks with no reports of adverse events (AEs) or serious adverse events (SAEs).

The β-Confident Registry was started in November 2009 to collect safety data as part of a post-approval commitment for canakinumab and comprises the largest documented CAPS cohort.[39] Patients are seen as per the local practice with no mandatory visits. Canakinumab dose is prescribed according to the local label, with no mandatory dose regimen. The registry aims to monitor the overall safety of canakinumab and to identify any new, serious drug reactions with a focus on special events including serious infections, vertigo, malignancies, and hypersensitivity reactions. The registry also aims to measure efficacy over time using the Physician's Global Assessment. There are 39 sites from 13 countries in Europe and the USA. Up to the cut-off of December 2014, 288 patients

were included, of which 109 were children; follow-up continued until December 2015.[39] An *NLRP3* mutation was diagnosed in 80% of patients, and 37% of patients were treated with canakinumab prior to enrolment in the registry. The incidence of AEs and SAEs were 105.1 and 15.0/100 patient-years, respectively. Infections, mostly upper respiratory tract infections, were the most commonly reported AEs with an incidence of 36.7/100 patient-years. The incidence of most AEs increased with increasing disease severity. Most SAEs were infections and were nervous system-related, mostly occurring in patients with NOMID. Nine events of neoplasms were reported by seven patients (incidence 1.3/100 patient-years). Twenty-eight events of vertigo were reported by 19 patients (incidence 3.9/100 patient-years), two of which were reported as SAEs. Interestingly, 13/18 patients who received a pneumococcal vaccination reported a post-injection local site reaction; 7 of these patients also had a fever, which was considered serious in 5 patients. All of these cases resolved spontaneously. Disease activity as measured by Physician's Global Assessment score remained absent or mild/moderate in most patients thoughout the 4-year follow-up. This sustained efficacy was also observed in patients without *NLRP3* mutation(s). Most patients remained stable over time, although some patients still demonstrated improvements after 4 years.

Outlook: Other IL-1 Driven Diseases Under Investigation and New Autoinflammatory Syndromes; What is New, What is Hot?

Professor Fabrizio De Benedetti

Colchicine is an efficacious treatment for FMF in many patients, however treatment-resistance does occur; while some patients do not respond, some patients may not tolerate an efficacious dose. Data from the Eurofever Registry show IL-1 inhibitors to be effective in colchicine-resistant patients with FMF, with similar results observed in patients with tumour necrosis factor receptor-associated periodic syndrome (TRAPS).[40] In addition, some patients with hyperimmunoglobulin D syndrome (HIDS) have been shown to respond to IL-1 inhibition.[40] The inflammasome interacts with a number of cellular pathways that may all lead to IL-1β overproduction, in addition to mutation in the *pyrin* gene. There are now proof-of-concept studies with canakinumab in colchicine-resistant familial Mediterrenaean fever (crFMF), TRAPS, and HIDS. A Phase II proof-of-concept study of canakinumab in crFMF involved three injections of open-label canakinumab 1 month apart in nine adults with a median attack rate of 1.2/month, most of whom had a poor condition as per the Physician's Global Assessment score criteria.[41,42] Most patients had a complete and satisfactory response, with an increase in attack severity during the follow-up period when the drug was withdrawn (Figure 2).[41]

A study of canakinumab in paediatric patients with severe crFMF (median 2.8 attacks/month) also demonstrated an improvement in Physician's Global Assessment score during treatment.[9] Similar studies in patients with TRAPS and HIDS have demonstrated improvements in Physician's Global Assessment score.[43,44] The safety results of these proof-of-concept studies were consistent with those observed in previous clinical trials and clinical practice are yet to be published. The results of the CLUSTER three-cohort, randomised, double-blind, placebo-controlled, Phase III study of canakinumab in patients with crFMF, TRAPS, or HIDS are awaited.[45]

There are a number of other diseases that may be categorised as IL-1 related, including Still's disease, Kawasaki disease, Behçet's disease, and cystinosis. There are few differences between SJIA and adult-onset Still's disease (AOSD), with the exception of sore throat, which is more commonly reported in AOSD.[46] The association with macrophage activation syndrome and response to treatment is similar in both conditions. A recent study has shown that many genes that are either downregulated or upregulated in patients with SJIA following treatment with canakinumab were upregulated or downregulated in patients with AOSD prior to canakinumab, respectively,[47] indicating that Still's disease may be a continuum from SJIA to AOSD.

Another study of children with recurrent pericarditis found that the median number of relapses per month fell from 0.46 to 0.01 following treatment with the IL-1 inhibitor anakinra (0.001).[48] There are a number of crystal-mediated diseases that may be linked to the inflammasome. Cystinosis is a rare autosomal recessive disorder caused by mutations or deletions in *CTNS* leading to lysosomal accumulation of cystine and formation of cystine crystals in the organs.[49-51] Low-grade inflammation due to crystals in the kidneys leads to kidney failure.

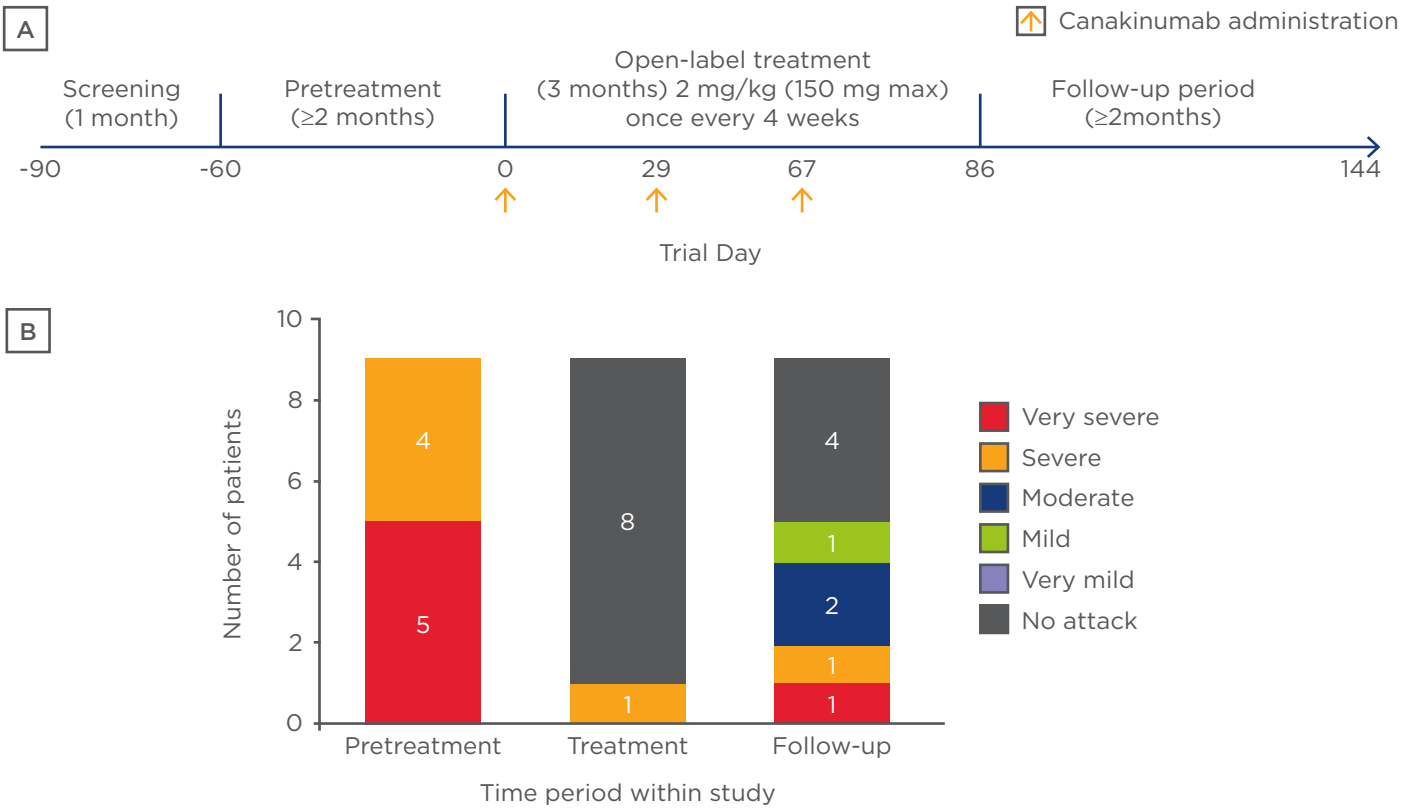

Figure 2: Attack severity in adults with colchicine-resistant familial mediterrenaean fever treated with canakinumab.[41]

a) Time frame of the proof-of-concept study; b) attack rate and severity in nine patients included in the proof-of-concept study.

Cystine crystals are phagocytosed by macrophages and induce IL-1β secretion.[52] *In vivo* data have shown evidence of activation of the inflammasome in patients through elevated IL-1β levels in peripheral blood mononuclear cells, and elevation of inflammasome markers in *CTNS* knockout mice.[52]

Summary

In summary, AI diseases are characterised by chronic inflammation secondary to marked dysregulation of the innate immune system. Information about the underlying genetic defects is increasing; the *NLRP3* inflammasome is directly involved in the pathogenesis of CAPS. IL-1 inhibition is an effective treatment in monogeneic AI diseases (e.g. CAPS, FMF, and TRAPS) and polygenic disease (e.g. SJIA). However, new AI diseases that do not involve the *NLRP3* inflammasome continue to pose a challenge. There is a clinical and biological rationale that the treat-to-target approach may improve outcomes in patients with JIA/SJIA. The JADAS and its cut-offs are well suited for use in clinical decision making as part of this strategy. Additional studies are needed to clarify the best strategy for improving outcomes in SJIA, such as the use of immunological and imaging-defined remission criteria, in addition to clinical criteria.

The long-term safety and efficacy observed with canakinumab in the β-Confident Registry are consistent with those observed in the clinical trial programme, with no new safety signals identified. Canakinumab was also found to be effective in *NLRP3* mutation-negative patients. In summary, real-world data show promising efficacy for IL-1 inhibition. Proof-of-concept trials have demonstrated efficacy and safety of canakinumab in crFMF, TRAPS, and HIDS, and the CLUSTER trial will provide evidence on these new indications for canakinumab. There is emerging evidence that AI diseases should be categorised by mediator/pathway.

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