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SYSTEMIC INTERLEUKIN 1β INHIBITION IN PROLIFERATIVE DIABETIC RETINOPATHY

A Prospective Open-Label Study Using Canakinumab

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Purpose: To evaluate the effect of systemic interleukin 1β inhibition using canakinumab (Ilaris) on retinal neovascularizations in proliferative diabetic retinopathy.

Methods: Patients with proliferative diabetic retinopathy were enrolled in a prospective uncontrolled pilot study. Canakinumab (150 mg) was given 3 times subcutaneously. The primary end point was the change in the area of neovascularization from baseline to Week 24. Secondary end points were the change in retinal edema measured and best-corrected visual acuity (BCVA), as well as systemic safety evaluation, HbA1c, and systemic inflammatory parameters.

Results: Systemic canakinumab treatment was well tolerated. None of the 8 eyes showed progression of neovascularizations within 24 weeks. Their mean size remained unchanged comparing 0.60 mm^2 at baseline with 0.62 mm^2 at Week 24 ($P = 0.944$). Median BCVA remained stable with 80 ETDRS letters at baseline and 82 ETDRS letters at Week 24. A not statistically significant reduction in retinal edema was detectable for the foveal central subfield thickness (mean, 313–295 μm). Mean HbA1c improved significantly from 7.92% to 7.30% within the 24 weeks ($P = 0.046$). Systemic inflammatory parameters remained overall unchanged.

Conclusion: Systemic canakinumab showed no change in neovascularizations in diabetic retinopathy. Promising effects were seen on diabetic macular edema.

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Diabetic retinopathy (DR) including diabetic macular edema (DME) is one of the leading causes for blindness in industrialized western countries and in the so-called emerging market countries. It is expected that demographic changes toward an older population worldwide will further contribute to a significant increase in DR. Today, DR affects more than four million U.S. Americans.[1,2]

Interleukin 1 (IL-1) consists of a group of cytokines that activate the expression of several pro-inflammatory genes. The 11 members of the IL-1 family of genes include IL-1β, as well as the antiinflammatory IL-1 receptor antagonist (IL-1Ra) that acts as a regulator of IL-1β signaling.[3] Inflammation has been recognized as an important contributor to β-cell dysfunction and apoptosis in patients with Type 2 diabetes mellitus (T2DM).[4] Specifically, IL-1β has been shown to induce β cell apoptosis in the pancreas.[5] Clinical studies using IL-1β inhibitors have shown improvement in glycemic control in subjects with Type 2 diabetes and a reduction of humoral inflammatory parameters.[6–8] Furthermore, IL-1β was detected in the vitreous of proliferative DR (PDR) while the IL-1Ra was lowered.[9,10]

Gevokizumab is one of the IL-1β inhibitors currently under investigation. It is currently also evaluated for noninfectious uveitis. A subgroup analysis of patients with a periodic ophthalmologic follow-up over 3 months in a Phase I dose-escalating study conducted with a single intravenous injection of gevokizumab in patients with T2DM with no-to-moderate nonproliferative DR did not reveal any safety issues.[6] Canakinumab is the IL-1β inhibitor evaluated in this study. Pooled data from 1026 T2DM patients treated with

canakinumab demonstrated that the medication was safe and well tolerated over a treatment period until 1.4 years at the evaluated doses.[8]

Canakinumab (Ilaris, Novartis Pharma Schweiz AG, Rotkreuz, Switzerland) is a human IgGκ monoclonal antibody targeting IL-1β that was primarily developed for the treatment of immune disorders. The drug was granted orphan drug status by both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency. In June 2009, the FDA approved canakinumab for treatment of cryopyrin-associated periodic syndromes. Today in Switzerland, canakinumab is approved—in addition to cryopyrin-associated periodic syndromes—for neonatal-onset multisystem inflammatory disease and for systemic juvenile idiopathic arthritis.[3] In the European Union also, the approval for gouty arthritis was obtained.

In addition to potential beneficial systemic effects of canakinumab in T2DM, an experimental model for ocular neovascularization indicated IL-1β inhibition to be a promising antiangiogenic treatment approach.[11] Because the systemic administration of full-length antiangiogenic IgG monoclonal antibodies has shown significant inhibition of choroidal neovascularization in humans, a prospective, uncontrolled open-label pilot study was designed to evaluate the effect of systemic IL-1β inhibition using canakinumab.[12]

Methods

Study Design

This prospective, single-center, uncontrolled open-label pilot study evaluated the safety and efficacy of canakinumab in subjects with PDR secondary to T1DM and T2DM. The study was approved by the affiliated ethics committee and the national regulatory authorities (Swissmedic). The study adhered to the tenets of the Declaration of Helsinki. A clinical trial registration was obtained (identifier NCT01589029 at ClinicalTrials.gov). All patients signed an informed consent before enrollment into the study. Ten patients were planned to be enrolled with an interim analysis being conducted after study completion of the fifth patient.

Study Population

Patients aged 18 years or older with stable T1DM or T2DM (in accordance with the American Diabetes Association diagnostic criteria) and evidence of an active PDR were enrolled. The retinal neovascularization, defined by fluorescein angiography (FA), had to be either non–high risk (neovascularization at disk [NVD], less than one-third disk area; neovascularization elsewhere [NVE], <½ disk area) or high risk with previous panretinal laser photocoagulation (PRP) and persistent activity. Key exclusion criteria were the need for laser coagulation or intravitreal therapy with steroids or anti-vascular endothelial growth factor (anti-VEGF) drugs for diabetic macular edema within the first 6 months after enrollment, or any of these treatments within 3 months before enrollment.

Intervention and Visit Schedule

All subjects received 150 mg subcutaneous injections of canakinumab (Ilaris) every 8 weeks for a total of 3 injections. The dose and the treatment intervals used were consistent with the currently approved dosing for cryopyrin-associated periodic syndromes. The treatment was administered at the Department of Ophthalmology at the City Hospital Triemli, Zurich. Patients were evaluated every 8 weeks. At every visit, a full ophthalmic examination including best-corrected visual acuity (BCVA) using the Early Treatment of Diabetic Retinopathy (ETDRS) charts, FA using the Heidelberg Retina Angiograph II (Heidelberg Engineering, Heidelberg, Germany), spectral domain optical coherence tomography (OCT) (Spectralis; Heidelberg Engineering), and fundus photography (Zeiss FF450, Oberkochen, Germany) were conducted. In addition, a physical examination, vital signs, blood samples, and urine analysis were part of the protocol at baseline and Week 24. A pregnancy test was conducted before enrollment in all women with childbearing potential. In case of progression of NVE/NVD, determined by FA, PRP was indicated as rescue treatment at any of the 8-weekly follow-up visits.

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Primary and Secondary End Points

The primary end point was defined as the change in size of retinal neovascularization (NVD and NVE) from baseline to 24 weeks of follow-up. All retinal neovascularizations were included in case they could be imaged by FA at baseline and Week 24. Images until 2 minutes were used to evaluate neovascularizations planimetrically. The planimetrical tool of the Heidelberg Eye Explorer (version 1.7.1.0; Heidelberg Engineering) was used to measure the total area of NVE/NVD in square millimeters. Regression of DME comparing baseline and Week 24 was one of the secondary end points being assessed by spectral domain OCT (512 A-scans, 20 × 15°) using parameters, such as foveal central point, foveal central subfield thickness, and total macular volume. In addition, the change in BCVA from baseline to 24 weeks and number of additional PRP were evaluated. Because canakinumab treatment was given systemically, HbA1c levels, systemic inflammatory markers (IL-6, IL-8, TNFα, hs-CRP, and serum amyloid A), and lipid profile (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglyceride) from baseline (Day 0 predose) to Week 24 were analyzed.

Statistical Analysis

For statistical analysis, the symmetric distributions of the differences were checked. The Wilcoxon signed-ranks test was used when distributions were symmetric. If distributions were not symmetric, the sign test was applied. The 2-sided significance level was set at $P = 0.05$. No correction for multiple testing was done. A Bonferroni correction was not considered because of relatively few cases in this pilot study.

Safety was assessed by recording adverse events, clinically significant abnormal changes in vital signs or laboratory values, and infusion reactions. An interim analysis was preplanned after study completion of the fifth patient.

Results

All 6 subjects, 5 men and 1 woman with a mean age of 66.2 years, enrolled in this pilot study completed the 4 visits as planned and received the scheduled 3 injections. All patients had T2DM.

In eight eyes of these six subjects, retinal neovascularization was detected; all of these were NVE, no NVD was recorded. Of these eight eyes, three were pretreated with PRP. The mean area of NVE at study entry was 0.60 mm^2 and 0.62 mm^2 after 24 weeks (P = 0.944). The primary end point was not met. At Weeks 8 and 16, NVE size was reduced to 0.50 mm^2 and 0.36 mm^2, respectively but did not reach statistical significance compared with baseline (P = 0.779 and P = 0.123, respectively). Figure 1 indicates no change in the mean area of NVE at all visits. Despite no regression in mean NVE area, all NVEs showed less leakage in late-frame FAs, which is shown for Patient 3 in Figure 2. For some eyes (Figure 3), stability of NVE size could be documented by spectral domain OCT. For all eyes (n = 12), median BCVA remained stable with 80 ETDRS letters (20/25) at baseline and 82 ETDRS letters (20/25^{+2}) at the end of the study. Of the 12 eyes, 8 eyes had evidence for DME with at least some cystoid intraretinal changes within the 20° × 15° spectral domain OCT scans. Optical coherence tomography measurements (n = 12) on all eyes changed as follows: mean foveal central point thickness reduced from 292 μm to 269 μm (P = 0.744), mean foveal central subfield thickness from 313 μm to 295 μm (P = 1.000), and mean total macular volume remained stable with 8.40 mm^3 and 8.41 mm^3 (P = 0.937) at study entry and after 24 weeks, respectively. Although no statistical significance was reached in any of the OCT parameters, OCT findings in several eyes showed remarkable regression (Figure 4).

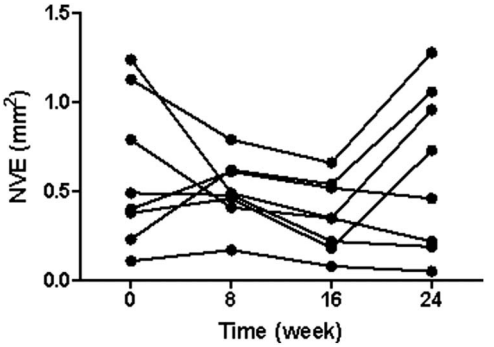

Fig. 1. Neovascularization elsewhere at baseline, Weeks 8, 16, and 24 (n = 8). Mean NVE dropped from 0.60 mm^2 at baseline to 0.50 mm^2 at Week 8 and 0.36 at Week 16, before increasing again to 0.62 at Week 24.

The changes in HbA1c, creatinine, inflammatory and lipid parameters are summarized in Table 1. Of these parameters, the change in HbA1c reached statistical significance. Levels of serum amyloid A, a protein of the apolipoprotein family that is mainly produced in the liver and associated with high-density lipoprotein, were analyzed. Some isoforms of serum amyloid A respond to inflammatory stimuli. As most of the samples were below the threshold of detection, no statistical assessment could be performed. Leukocyte levels showed no overall significant change, and each of the six patients had no clinically relevant change in their leukocyte count over the course of the study.

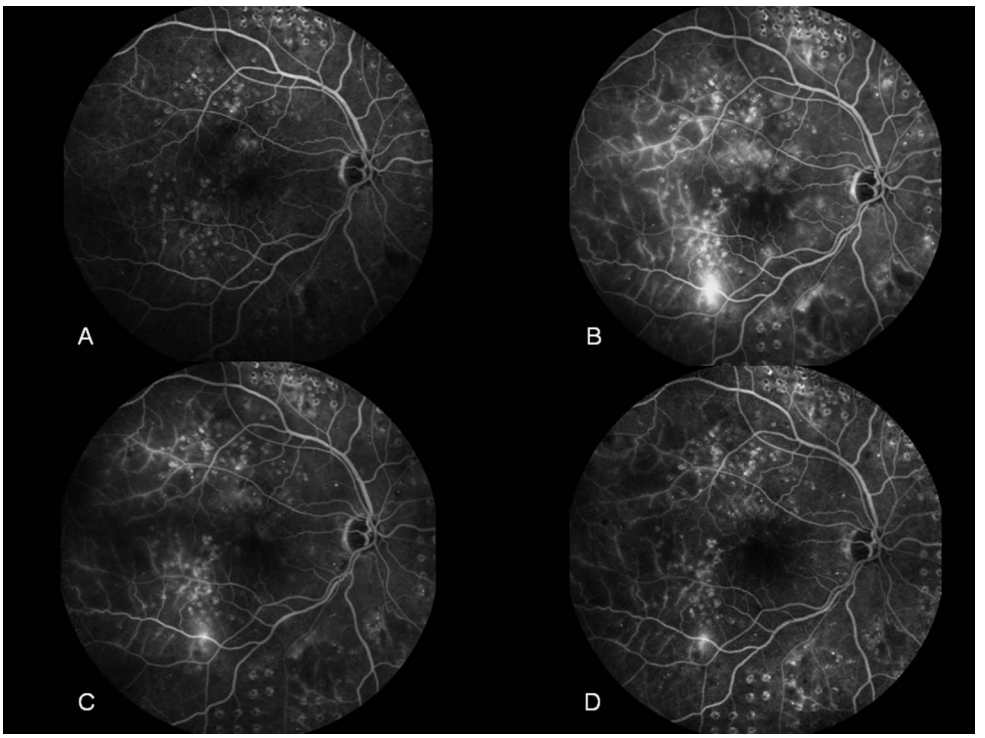

Fig. 2. Patient 3. **A.** Fluorescein angiography 7 months before enrollment into the study. **B.** Fluorescein angiography at baseline showing new hypoperfusion and increased perivascular leakage in the temporal macula and new NVE. **C.** Fluorescein angiography at Week 24 (8 weeks after the third subcutaneous canakinumab injection) shows that perivascular and NVE-associated leakage is reduced. **D.** Fluorescein angiography 4 months after the end of the study (no further treatment) shows no relevant change to Week 24.

The safety profile was unremarkable. All canakinumab subcutaneous injections were well tolerated and without local side effects. During the study, four adverse events in three different subjects occurred: three nonserious and one serious. None of them was classified by the treating physician as possibly related to the study medication. One patient suffered from pain in his left arm 4 days before the first canakinumab injection. The adverse event was not considered to be associated with the screening examination. Superficial vein thrombosis occurred in the same patient approximately 4 months later, 7 weeks after the second injection, and needed treatment with subcutaneous nardoparin, a low–molecular weight heparin, and local heparin gel for 8 weeks. The patient has had a history of varicosis. A second patient developed bronchitis 3 weeks after the first injection but did not need any medical treatment. Because no infectious cause became evident and the patient had a history of recurrent bronchitis due to chronic obstructive pulmonary disease, the treating physician did not consider bronchitis related to canakinumab. Retrospectively,

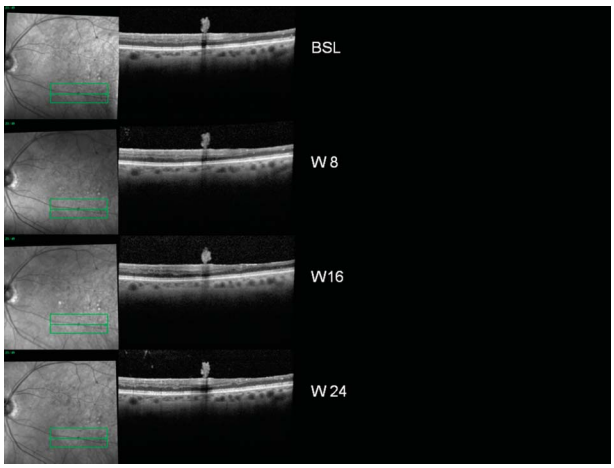

Fig. 3. Spectral domain optical coherence tomography of Patient 1 shows no change in retinal NVE over 24 weeks. BSL, baseline.

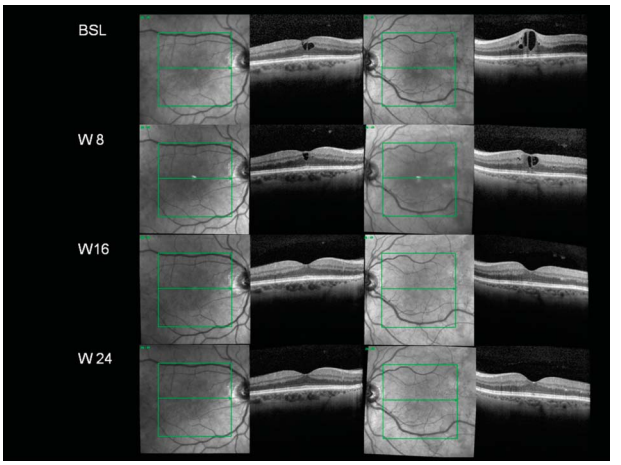

Fig. 4. Spectral domain optical coherence tomography of the right and left eyes of Patient 5 showing subfoveal intraretinal cystoid spaces in both eyes. At Week 8, changes have regressed bilaterally and have disappeared at Weeks 16 and 24. BSL, baseline.

Table 1. Systemic Laboratory Parameters at Baseline and to Week 24

	Baseline	24 Weeks	*P*	n
HbA1c, %	7.92	7.3	0.046	6
hs-CRP, mg/L	1.18	1.17	1.000	6
leukocyte count, 10^9/L	7.09	6.85	0.600	6
TNFα, pg/mL	2.7	2.24	0.375	5
IL-8, pg/mL	35	216	1.000	6
IL-6, pg/mL	3.36	4.5	0.375	6
Total cholesterol, mmol/L	4.32	4	0.138	6
HDL, mmol/L	1.35	1.43	0.207	6
LDL, mmol/L	2.42	2.17	0.225	6
Triglyceride, mmol/L	1.76	1.55	0.173	6
Creatinine, μmol/L	81	73	1.000	6

HDL, high-density lipoprotein; hs-CRP, highly sensitive C-reactive protein; IL-6/8, interleukin 6/8; LDL, low-density lipoprotein; TNFα, tumor necrosis factor alpha.

a relation to treatment cannot be ruled out with certainty. Finally, the third patient developed symptomatic cholecystolithiasis 25 days after the second injection and was treated by cholecystectomia 2 days later (reported as Serious Adverse Event for hospitalization). The cholecystolithiasis was known before enrollment into the study, and the need for surgery had been expected. None of the rare but known potentially IL-1β associated adverse events (infectious diseases, hypersensitivity reactions, neutropenia) were seen in the study.

Discussion

This first prospective study on systemic IL-1β inhibition using canakinumab in patients with PDR did not show a significant reduction of the area of retinal neovascularizations assessed by FA in the preplanned interim analysis. However, promising effects were seen on DME over 24 weeks' duration of the study. Unfortunately, the study was not designed to evaluate the effect of canakinumab on DME. Primarily, patients with PDR were selected who did not have DME involving the fovea associated with vision loss. Fovea involving DME with vision loss was an exclusion criterion because it would have required approved anti-VEGF treatment in Switzerland. This treatment would have interfered with the primary end point of the study.

No regression of NVEs was seen, which is in discordance with the preclinical study indicating an antiangiogenic effect in the corneal neovascularization model.[11] The absence of regression of NVEs might have various reasons. First, the 8 weekly subcutaneous injection of 150 mg canakinumab might be insufficient to induce NVE regression. Today, 300 mg of canakinumab every 4 weeks is also approved for the treatment of the systemic juvenile idiopathic arthritis. This treatment regimen was not approved at the initiation of the study. It could be concluded that drug dose of 150 mg was just sufficient to stabilize NVEs (none of the NVEs progressed under treatment) but was too low to induce NVE regression. Patient 2 showed an area with preneovascular changes (Intraretinal Microvascular Abnormaility) that regressed under treatment with canakinumab (Figure 5). This could indicate that canakinumab in the used systemic dose and treatment interval is sufficient to induce regression of preneovascular changes and to stabilize NVE but is insufficient to lead to NVE regression. Second, the systemic administration might not be appropriate to bring enough drugs to the retinal circulation. This argument seems rather unlikely because all NVEs in the study showed less leakage in late frames of FA, some effect

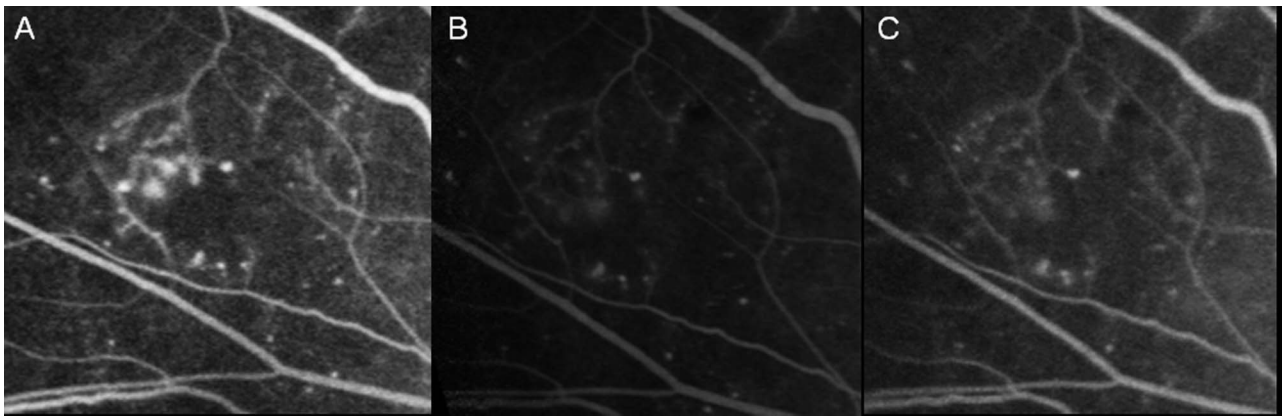

Fig. 5. Fluorescein angiography of Patient 2 showing zone of nonperfusion nasal superior to the disk. **A.** At baseline, preproliferative changes appear as small hyperfluorescent lesions at the edge of the zone of nonperfusion. At Week 16 (**B**) and Week 24 (**C**), FA indicates almost complete regression of preproliferative changes.

on macular edema was detected, and other full-length antibodies have been shown to effectively inhibit ocular neovascularizations.[12] Third, some of the treated eyes had previous PRP; therefore, the study may have selected "matured" NVEs less likely to respond to any antiangiogenic treatment (n = 3/8). However, the subgroup without previous treatment (n = 5/8) did not show NVE regression either. The authors consider the most likely reason for this finding as the insufficient antiangiogenic effect of canakinumab. Some analogies may be drawn with steroid treatment, which demonstrated antiangiogenic effects in preclinical studies but has not shown monotherapy as a convincing antiangiogenic effect in ocular neovascularizations in humans.[13]

At the initiation of the study, very limited information was available on a potential antileakage effect of canakinumab in preclinical studies. The best evidence in that context was that IL-1β was found to accelerate apoptosis of retinal capillary cells and endothelial cell loss in bovine retina, especially in high-glucose conditions. The use of an IL-1Ra led to significantly reduced glucose-induced abnormalities and apoptosis in bovine retina.[14] To our interest, we found regression or resolution of edema in most eyes with DME. As mentioned earlier, the study was not designed to evaluate the effect on DME because foveal edema associated with vision loss was an exclusion criterion. This explains why an effect was numerically detectable in two OCT parameters evaluated but did not reach statistical significance. The study was not controlled; therefore, a beneficial effect by chance or because of better glycemic control cannot be excluded. In any case, the effect on the DME shows a slower onset than that we are used to with anti-VEGF agents or intravitreal steroids (Figure 4). This could indicate that a higher and more frequent dosing regimen might be beneficial. In addition to the delayed onset, a prolonged inhibitory effect on leakage was seen in some eyes more than 6 months after the last subcutaneous injection. Whether this could imply longer treatment durability requires further study.

In general, the last years have shown that local intraocular therapy is preferred over systemic treatment for exudative macular diseases. Systemic anti-VEGF therapy for neovascular age-related macular degeneration has been associated with an increased blood pressure.[12,15] Systemic anti-VEGF therapy, in addition to chemotherapy in patients with malignant tumors, goes along with an increased risk, especially hypertension.[16] For intraocular anti-VEGF therapy, a convincing systemic safety signal has not been shown.[17] However, systemic treatment has potential advantages, especially in frequent binocular diseases such as diabetic macular edema. The perception of systemic therapy may change, if a systemically applied drug has rather beneficial systemic effects than systemic risks. A recent meta-analysis of prospective controlled clinical trials in diabetic patients indicated canakinumab to be safe and well-tolerated over a treatment period of until 1.4 years.[8] But there is even some evidence that systemic canakinumab is not only safe but could provide relevant systemic benefits. The most intriguing is the improvement in HbA1c with systemic IL-1β inhibition, which was not only shown in our small study to be significant but also in larger controlled clinical trials.[7,8] Increased blood sugar is, in addition to the duration of the disease, the key risk factor for DR as well as diabetic nephropathy, neuropathy, and albuminuria.[18] In this context, improved HbA1c by IL-1β inhibition could be of benefit not only for prevention or stabilization of DR but also for other organs affected by the disease. In addition, IL-1β inhibition has been associated with improved inflammatory and cardiovascular parameters.[19,20] It is even considered that canakinumab could reduce the risk for cardiovascular events in patients at risk, which is currently evaluated in the canakinumab antiinflammatory thrombosis outcomes study.[21]

In conclusion, repeated systemic administration of canakinumab showed stabilization but no regression of retinal neovascularizations in patients with PDR. Reduced leakage from NVE and reduced macular edema were found in most patients. In combination with potentially improved, systemic, glycemic, and inflammatory control and early evidence for a risk reduction for cardiovascular events, systemic IL-1β inhibition warrants further study, especially for DME.

Key words: antiangiogenic, interleukin, canakinumab, diabetic retinopathy, neovascularization, edema.

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References

1. Kempen JH, O'Colmain BJ, Leske MC, et al. The prevalence of diabetic retinopathy among adults in the United States. Arch Ophthalmol 2004;122:552–553.
2. Ramachandran A, Mary S, Yamuna A, et al. High prevalence of diabetes and cardiovascular risk factors associated with urbanization in India. Diabetes Care 2008;31:893–898.
3. Dhimolea E. Canakinumab. MAbs 2010;2:3–13.
4. Maedler K, Sergeev P, Ris F, et al. Glucose-induced β-cell production of IL-1β contributes to glucotoxicity in human pancreatic islets. J Clin Invest 2002;110:851–860.

5. Schumann DM, Maedler K, Franklin I, et al. The Fas pathway is involved in pancreatic beta cell secretory function. Proc Natl Acad Sci U S A 2007;104:2861–2866.
6. Cavelti-Weder C, Babians-Brunner A, Keller C, et al. Effects of gevokizumab on glycemia and inflammatory markers in type 2 diabetes. Diabetes Care 2012;35:1654–1662.
7. Larsen CM, Faulenbach M, Vaag A, et al. Interleukin-1-receptor antagonist in type 2 diabetes mellitus. N Engl J Med 2007; 356:1517–1526.
8. Howard C, Noe A, Skerjanec A, et al. Safety and tolerability of canakinumab, an IL-1β inhibitor, in type 2 diabetes mellitus patients: a pooled analysis of three randomised double-blind studies. Cardiovasc Diabetol 2014;13:94.
9. Patel JI, Saleh GM, Hykin PG, et al. Concentration of haemodynamic and inflammatory related cytokines in diabetic retinopathy. Eye (Lond) 2008;22:223–228.
10. Demircan N, Safran BG, Soylu M, et al. Determination of vitreous interleukin-1 (IL-1) and tumour necrosis factor (TNF) levels in proliferative diabetic retinopathy. Eye (Lond) 2006;20:1366–1369.
11. Lu P, Li L, Liu G, et al. Enhanced experimental corneal neovascularization along with aberrant angiogenic factor expression in the absence of IL-1 receptor antagonist. Invest Ophthalmol Vis Sci 2009;50:4761–4768.
12. Michels S, Rosenfeld PJ, Puliafito CA, et al. Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration twelve-week results of an uncontrolled open-label clinical study. Ophthalmology 2005;112:1035–1047.
13. McNatt LG, Weimer L, Yanni J, Clark AF. Angiostatic activity of steroids in the chick embryo CAM and rabbit cornea models of neovascularization. J Ocul Pharmacol Ther 1999;15: 413–423.
14. Kowluru RA, Odenbach S. Role of interleukin-1beta in the pathogenesis of diabetic retinopathy. Br J Ophthalmol 2004; 88:1343–1347.
15. Geitzenauer W, Michels S, Prager F, et al. Comparison of 2.5 mg/kg and 5 mg/kg systemic bevacizumab in neovascular age-related macular degeneration: twenty-four week results of an uncontrolled, prospective cohort study. Retina 2008;28:1375–1386.
16. Galfrascoli E, Piva S, Cinquini M, et al. Risk/benefit profile of bevacizumab in metastatic colon cancer: a systematic review and meta-analysis. Dig Liver Dis 2011;43:286–294.
17. Moja L, Lucenteforte E, Kwag KH, et al. Systemic safety of bevacizumab versus ranibizumab for neovascular age-related macular degeneration. Cochrane Database Syst Rev 2014;9: CD011230.
18. The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. Diabetes 1995;44:968–983.
19. Ikonomidis I, Tzortzis S, Andreadou I, et al. Increased benefit of interleukin-1 inhibition on vascular function, myocardial deformation, and twisting in patients with coronary artery disease and coexisting rheumatoid arthritis. Circ Cardiovasc Imaging 2014;7:619–628.
20. Ridker PM, Howard CP, Walter V, et al. Effects of interleukin-1β inhibition with canakinumab on hemoglobin A1c, lipids, C-reactive protein, interleukin-6, and fibrinogen: a phase IIb randomized, placebo-controlled trial. Circulation 2012;126: 2739–2748.
21. Ridker PM, Thuren T, Zalewski A, Libby P. Interleukin-1β inhibition and the prevention of recurrent cardiovascular events: rationale and design of the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS). Am Heart J 2011;162:597–605.