Canakinumab Study Group; Pickersgill, Linda; de Koning, Eelco; Ziegler, Anette-G; Böehm, Bernhard; Badenhoop, Klaus; Schloot, Nanette; Bak, Jens Friis; Pozzilli, Paolo; Mauricio, Didac; Donath, Marc Y; Casteño, Luis; Wägner, Ana; Lervang, Hans Henrik; Perrild, Hans; Mandrup-Poulsen, Thomas; AIDA Study Group; Colman, P; Wentworth, J; Wherrett, D; Simell, O; Bosi, E; Roncarolo, M G; Bingley, P; Peakman, M; Thomas, St; Skyler, J S; Anderson, M; Gitelman, S; Atkinson, M; Clare-Salzler, M; Schatz, D; Winter, W; Bourcier, K; Becker, D; Trucco, M; Blum, J; DiMeglio, L; Buckner, J; Chase, H P; Eisenbarth, G S; Gottlieb, P; Fathman, C G; Wilson, D M; Goland, R; Grave, G; Greenbaum, C; Hering, B; Moran, A; Herold, K; Sherwin, R; Insel, R; Krischer, J P; Marks, J; Pugliese, A; Palmer, J P; Raskin, P; Siegelman, M; Russell, W; Thomas, J; Fradkin, J; Leschek, E; Spain, L; Savage, P; Harrison, L; Mahon, J; Nanto-Salonen, K; Ziegler, A; Benoist, C; Orban, T; Bluestone, J; Brown, D; Wagner, J; Cowie, C; Jordan, S; Kaufman, F R; Parkman, R; Lachin, J M; Nepom, G; Pescovitz, M; Rodriguez, H; Peyman, J; Ridge, J; Skyler, J S; Bourcier, K; Greenbaum, C J; Krischer, J P; Leschek, E; Savage, P; Spain, L; Rafkin, L; Cowie, C; Malozowski, S; Foulkes, M; Krause-Steinrauf, H; Lachin, J M; Zafonte, S J; Peyman, J; Ridge, J; Skyler, J S; Greenbaum, C J; Kenyon, N S; Rafkin, L; Santiago, I; Sosenko, J;
Interleukin-1 antagonism in type 1 diabetes of recent onset: two multicentre, randomised, double-blind, placebo-controlled trials.

Innate immunity contributes to the pathogenesis of autoimmune diseases, such as type 1 diabetes, but until now no randomised, controlled trials of blockade of the key innate immune mediator interleukin-1 have been done. We aimed to assess whether canakinumab, a human monoclonal anti-interleukin-1 antibody, or anakinra, a human interleukin-1 receptor antagonist, improved β-cell function in recent-onset type 1 diabetes. We did two randomised, placebo-controlled trials in two groups of patients with recent-onset type 1 diabetes and mixed-meal-tolerance-test-stimulated C peptide of at least 0·2 nM. Patients in the canakinumab trial were aged 6-45 years and those in the anakinra trial were aged 6-45 years. Participants and carers were masked to treatment assignment. The primary endpoint was baseline-adjusted 2-h area under curve C-peptide response to the mixed meal tolerance test at 12 months (canakinumab trial) and 9 months (anakinra trial). Analyses were by intention to treat. These studies are registered with ClinicalTrials.gov, numbers NCT00947427 and NCT00711503, and EudraCT number 2007-007146-34. Patients were enrolled in the canakinumab trial between Nov 12, 2010, and April 11, 2011, and in the anakinra trial between Jan 26, 2009, and May 25, 2011. 69 patients were randomly assigned to canakinumab (n=47) or anakinra (n=35) or placebo (n=22) monthly for 12 months and 69 were randomly assigned to anakinra (n=35) or placebo daily for 9 months. No interim analyses were done. 45 canakinumab-treated and 21 placebo-treated patients in the canakinumab trial and 25 anakinra-treated and 26 placebo-treated patients in the anakinra trial were included in the primary analyses. The difference in C peptide area...
under curve between the canakinumab and placebo groups at 12 months was 0.01 nmol/L (95% CI -0.11 to 0.14; p=0.86), and between the anakinra and the placebo groups at 9 months was 0.02 nmol/L (-0.09 to 0.15; p=0.71). The number and severity of adverse events did not differ between groups in the canakinumab trial. In the anakinra trial, patients in the anakinra group had significantly higher grades of adverse events than the placebo group (p=0.018), which was mainly because of a higher number of injection site reactions in the anakinra group. Canakinumab and anakinra were safe but were not effective as single immunomodulatory drugs in recent-onset type 1 diabetes. Interleukin-1 blockade might be more effective in combination with treatments that target adaptive immunity in organ-specific autoimmune disorders. National Institutes of Health and Juvenile Diabetes Research Foundation.

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