DIABETES/METABOLISM RESEARCH AND REVIEWS
Diabetes Metab Res Rev 2009; **25**: 321–324.
Published online in Wiley InterScience (www.interscience.wiley.com) **DOI:** 10.1002/dmrr.960

REVIEW ARTICLE

The anti-interleukin-1 in type 1 diabetes action trial – background and rationale

Linda M.S. Pickersgill[1]
Thomas R. Mandrup-Poulsen[1,2*†]

[1]*Steno Diabetes Center and Hagedorn Research Institute, DK-2820 Gentofte, Denmark*

[2]*Center for Medical Research Methodology, Institute of Biomedical Sciences, Faculty of Health Sciences, University of Copenhagen, DK-2200 Copenhagen N, Denmark*

*Correspondence to: Thomas R. Mandrup-Poulsen, DMSc, Hagedorn Research Institute, Niels Steensensvej 1, DK-2820 Gentofte, Denmark.
E-mail: tmpo@hagedorn.dk

Received: 23 December 2008
Accepted: 10 March 2009

Summary

Type 1 diabetes (T1D) is caused by an inflammatory destruction of pancreatic beta-cells. Pro-inflammatory cytokines, in particular interleukin-1 (IL-1), have been suggested to be effector molecules based on the observations that pro-inflammatory cytokines cause beta-cell apoptosis *in vitro* and aggravate diabetes *in vivo*, and that inhibition of the action of these cytokines reduce diabetes incidence in animal models of type 1 diabetes and islet graft destruction. This review presents the rationale for and design of a recently launched double-blind, multicenter, randomized clinical trial that investigates the effect of interleukin-1 antagonism on beta-cell function in subjects with T1D of recent-onset. Copyright © 2009 John Wiley & Sons, Ltd.

Keywords inflammation; metabolism; anakinra; cytokines; beta-cell function.

Introduction

The aim of this review is to present the background and rationale of a randomized double-blinded clinical trial that started in January 2009 with the purpose to test the feasibility, safety and potential efficacy of interleukin-1 (IL-1) receptor blockade in recent-onset type 1 diabetic patients.

IL-1 – a proinflammatory cytokine

The cytokine IL-1 is produced by most cells provided appropriate stimulation, but especially by monocytes, macrophages, dendritic cells and endothelium in response to stimuli such as endotoxins, exotoxins and other cytokines [1]. IL-1 functions as a proinflammatory signal molecule and mediates the acute phase response in infection, inflammation, tissue trauma and stress as well as in autoinflammatory disorders related to defects in the inflammasome that processes pro-IL-1 to mature IL-1. IL-1 has also been implied in the development of organ-specific auto-immune diseases [2]. IL-1 has direct effect on blood vessels, causing vasodilation [3], and exerts indirect effects through stimulation of other immune system cells [1,3].

Blocking the effect of IL-1

There are several principles by which the activity of IL-1 can be modulated: prevention of IL-1 processing and secretion by inhibitors of IL-1ß converting enzyme, caspase-1; blocking IL-1 binding to its receptors by IL-1 receptor antagonist (IL-1Ra), IL-1 receptor accessory protein antibodies or IL-1 receptor type 1 antibodies; or capture of IL-1 by soluble forms of IL-1R or IL-1 receptor accessory protein or anti–IL-1ß monoclonal antibodies and more recently IL-1 Trap [4]. Although these compounds all prevent IL-1

action, they have different biological profiles [4]. Thus, over-expression of IL-1Ra blocks nuclear factor kB (NFkB) signalling in both B and T lymphocytes while soluble IL-1 receptor accessory protein spares T lymphocytes [5]. Although only IL-1Ra and the IL-1 Trap have been approved by the Food and Drug Administration in the USA for rheumatoid arthritis and auto-inflammatory diseases, several compounds are being investigated in clinical trials for other immune diseases. Some compounds have a half-life of several days to weeks, allowing for weekly or bimonthly injections. Furthermore, the local injection-site reaction observed in 20–50% patients treated with IL-1Ra [6–8] is less pronounced or not observed for the more recently developed compounds. These novel compounds not only increase convenience and coverage but also raise a potential safety concern in case of intercurrent severe infectious disease where rapid reversal of IL-1 blockade might be desirable. This is not an issue with IL-1Ra that has a half-life of 4–6 h.

In vitro and animal experience with anti-IL-1 in diabetes models

For 20 years, it has been recognized that IL-1 is selectively cytotoxic to rodent and human beta-cells *in vitro* [1,9–12] and anti-IL-1 therapies reduce diabetes incidence in animal prevention models [1]. IL-1 alone or in combination with other inflammatory cytokines causes beta-cell destruction in rodent and human islets and in perfused pancreas via the mitogen activated protein kinase and NFkB signalling pathways, IL-1 given intraperitonially to non-diabetes prone animals causes transient insulinopenic diabetes, IL-1 is expressed early in non-obese diabetic islets, anti-IL-1 intervention prevents diabetes development in models of type 1 diabetes and islet graft destruction, and transgenic mice with knockout of the IL-1 receptor reduces diabetes incidence by 30% [1,12]. We recently reported that 13 weeks of IL-1Ra therapy improved glycaemia and beta-cell function in type 2 diabetes, a disorder in which glucose-induced beta-cell apoptosis may be IL-1 dependent [6]. IL-1Ra has been used in >100 000 patients with rheumatoid or inflammatory diseases and the intervention is remarkably safe [6,7,8]. Taken together, this evidence supporting a role for IL-1 in the pathogenesis in type 1 diabetes and the safety of the drug prompted the testing of the effects of IL-1Ra in type 1 diabetes. Considering the surprising efficacy observed in type 2 diabetes [6] and the solid rationale for the use of anti-IL-1 in type 1 diabetes [1,9–12], we reasoned that clinical benefit to new-onset type 1 diabetes from anti-IL-1 therapy is likely to be expected.

Experience of the drug in other disease conditions

Since November 2001, when the Food and Drug Administration approved recombinant human IL-1Ra (anakinra) for treatment of rheumatoid arthritis, it has been widely used as part of clinical practice in rheumatoid arthritis in >100 000 patients [7,8]. Anakinra has also shown striking efficacy in the treatment of severe-onset juvenile idiopathic arthritis and rare autoinflammatory disease related to mutations in the inflammasome leading to constitutive IL-1 processing, such as Muckle–Wells syndrome [13,14].

The pathogenesis of several inflammatory diseases has been linked to IL-1, but its role has not yet been firmly established (see Table 1).

Anakinra and type 2 diabetes

In a randomized trial [6], 70 type 2 diabetes mellitus (T2DM) patients were treated for 13 weeks with 100 mg anakinra once daily or placebo. The results showed lowering of HbA_{1c}, IL-6, C-reactive protein and proinsulin-to-insulin ratio as well as higher C-peptide secretion when comparing the anakinra treated group with the placebo group.

The T2DM study provided proof-of-principle that IL-1 is an important mediator of impaired glycaemia in type 2 diabetes by affecting beta-cell function. The results also suggested that long-term inhibition of IL-1 action may preserve beta-cell function in type 2 and type 1 diabetic patients.

Table 1. IL-1 and inflammatory disease

Disease	Effect of antagonising IL-1	Reference
Rheumatoid arthritis	+	7,8,15
Systemic onset juvenile idiopathic arthritis	+	13
T2DM	+	6
Muckle–Wells syndrome	+	13,14
Sepsis	Reduced mortality rate	3
Inflammatory bowel disease	Ongoing clinical trial	3
Chronic and acute myeloid leukaemia	Pathogenesis linked to IL-1	3
Atherosclerosis	Pathogenesis linked to IL-1	3
Transplant rejection reaction	Pathogenesis linked to IL-1	3
Graft-*versus*-host disease	Pathogenesis linked to IL-1	3
Psoriasis	Pathogenesis linked to IL-1	3
Asthma	Pathogenesis linked to IL-1	3
Osteoporosis	Pathogenesis linked to IL-1	3
Periodontosis	Pathogenesis linked to IL-1	3
Auto-immune thyroiditis	Pathogenesis linked to IL-1	3
Alcoholic hepatitis	Pathogenesis linked to IL-1	3
Preterm labour after uterine infection	Pathogenesis linked to IL-1	3
Sleep disorders	Pathogenesis linked to IL-1	3
Familial cold autoinflammatory syndrome	+	14
Neonatal-onset multisystem inflammatory disease	+	14

DOI: 10.1002/dmrr

Recombinant human IL-1Ra, anakinra – biology and indications

Anakinra is a recombinant, non-glycosylated form of the human IL-1Ra. It differs from native human IL-1Ra in that it has the addition of a single methionine residue to its amino terminus, and it is produced by recombinant DNA technology using an *E. coli* bacterial expression system. Anakinra blocks the biologic activity of IL-1 by competitively inhibiting IL-1 binding to the IL-1 type I receptor, which is expressed in a wide variety of tissues and organs [15].

Anakinra is indicated for the reduction in signs and symptoms and slowing the progression of structural damage in moderately to severely active rheumatoid arthritis, in patients 18 years of age or older who have failed one or more disease modifying antirheumatic drugs and in the autoinflammatory cryopyrin-associated periodic syndromes. Anakinra can be used alone or in combination with disease modifying antirheumatic drugs other than tumour necrosis factor blocking agents.

Long-term safety has been assessed in trials with treatment up to 1.5 years [16] and no increase in adverse events with prolonged treatment could be found. Injection-site reactions were the only side effect that could be related to treatment [16].

The AIDA study: aim, hypothesis and design

The aim of the anti-interleukin-1 in diabetes action (AIDA) trial is to test the feasibility, safety/tolerability and potential efficacy of anti-IL-1 therapy in maintaining or enhancing beta-cell function in people with new-onset type 1 diabetes. The hypothesis is that anti-IL-1 treatment as add-on therapy to conventional insulin therapy will preserve or enhance residual beta-cell function. We have chosen anakinra for this study based on proven safety, known efficacy and availability [7,8].

AIDA has a randomized, placebo-controlled, double-masked, parallel-group, multi-centre design. The patients are instructed to administer anti-IL-1 therapy in the form of anakinra (Kineret®, Amgen, CA, USA) [4] at a dose of 100 mg once daily or placebo by subcutaneous injection at the same time point in the morning. Primary and secondary endpoints are investigated every 3 months, and safety parameters after 1 month and then every 3 months. Serum IL-1Ra levels will be measured every 3 months for compliance monitoring.

To facilitate interpretation of a difference in C-peptide levels between groups, it is important that the patients strive for optimization of glycaemic control and that an identical target is achieved in the two groups [17]. It is recognized that optimizing glycaemia may reduce glucose-induced IL-1 secretion from islets and thereby reduce a potential effect exerted by IL-1 antagonism directed against this mechanism, but we do not find repeating the design of the study carried out in type 2 diabetes maintaining anti-diabetic therapy unchanged, in this case in new-onset type 1 diabetic patients medically or ethically defendable. Randomization and blinding is performed by an independent data monitoring unit.

The primary endpoint is difference in C-peptide responses to a standardized 2-h mixed-meal test (Boost) between the two treatment groups. Secondary endpoints include changes in incremental and/or peak C-peptide response, time to peak C-peptide, change in insulin requirement per kilogram body weight per day, frequency of insulin-free state with maintenance of $HbA_{1c}<7.5\%$, HbA_{1c} and fasting plasma glucose (FPG) (although as mentioned investigators should strive to optimize glycaemia to the same level in both treatment arms), and circulating IL-6 and C-reactive protein.

Other ongoing trials in blocking the IL-1-effect in T1DM and T2DM

A study of the effect of daily injections of anakinra in children with newly diagnosed T1DM is being planned [18]. Fifteen patients will be recruited for this efficacy study.

Two studies of XOMA52, an IL-1-antibody with a half-life of 22 days, have been initiated and are planned to enrol 36 T2DM patients each [19]. This drug has the potential for once per month injections [20]. Interim results from 48 patients followed for 3 months (40 treated with XOMA52 and 8 with placebo) have shown reduced HbA_{1c} and serum C-reactive protein, and an increase in the insulin production at 28 days after a single dose of XOMA52 compared with baseline, and with no change in the placebo group [20]. Eli Lilly reported proof of concept in diabetes with an IL-1ß antibody, and plans a phase 2 study. Novartis has initiated a phase 2 trial in type 2 diabetes with an IL-1ß antibody, and is planning a phase 2 trial in recent-onset type 1 diabetes with this antibody.

Perspectives

Proof-of-principle coming from these studies may have significant impact on the treatment of type 1 diabetes and may open perspective for primary prevention in risk individuals as well as in clinical islet transplantation.

Acknowledgements

This study was supported by JDRF grant # 8-2007-481, Øresund Diabetes Academy, Steno Diabetes Center, Novo Nordisk A/S. Study drug is provided by Amgen.

Conflict of interest

The authors have no conflicts of interest.

DOI: 10.1002/dmrr

†On behalf of the AIDA study group:

Investigators

Thomas R. Mandrup-Poulsen, Hagedorn Research Institute and Steno Diabetes Center, Gentofte, Denmark (investigator and sponsor);
Linda M.S. Pickersgill, Hagedorn Research Institute and Steno Diabetes Center, Gentofte, Denmark (coordinating investigator);
Ulla Bjerre Christensen, Steno Diabetes Center, Gentofte, Denmark;
Henrik Ullits Andersen, Steno Diabetes Center, Gentofte, Denmark;
Lise Tarnow, Steno Diabetes Center, Gentofte, Denmark;
Jens Friis Bak (PI) and Jørgen Rungby, Aarhus University Hospital, Aarhus, Denmark;
Peter C. Eskildsen, Köge Hospital, Köge, Denmark;
Hans-Henrik Lervang, Aalborg University Hospital, Aalborg, Denmark;
Hans Perrild, Bispebjerg University Hospital, Copenhagen, Denmark;
Birger Thorsteinsson (PI) and Ulrik Pedersen-Bjerregaard, Nordsjaellands Hospital, Hillerod, Denmark;
Klaus Badenhoop (PI), Maria Sandler and Gesine Meyer, University Hospital Frankfurt am Main, Germany;
Bernhard Böhm (PI), Silke Rosinger and Erika Thanner, University of Ulm, Germany;
Nanette Schloot (PI) and Bettina Rose, Heinrich-Heine University, Düsseldorf, Germany;
Anette Ziegler (PI) and Markus Walter, Institut für Diabetes Forschung, Munich, Germany;
Nora Hosszúfalusi (PI) and Tamas Gabler, Semmelweis Medical School, Budapest, Hungary;
Paolo Pozzilli (PI) and Chiara Guglielmi, University Campus Bio-Medico, Rome, Italy;
Vaidotas Urbanavicius, Vilnius University Hospital, Vilnius, Lithuania;
Eelco de Koning (PI), Bart Roep, Hanno Pijl and Fleur Kleijwegt, Leiden University Medical Center, Leiden, The Netherlands;
Adam Kretowski (PI) and Anna Okruszko, Department of Endocrinology, Medical University of Bialystok, Poland;
Tadej Battelino, Department of Pediatric Endocrinology, University Children's Hospital, Ljubljana, Slovenia;
Sonia Gaztambide (PI), Luis Castaño and Federico Vasquez, Hospital de Cruces, Bilbao, Spain;
Jose Cubero Marcos (PI) and Esther Arnaldo, Hospital Santa Creu i Sant Pau, Barcelona, Spain;
Didac Mauricio (PI) and Marta Garcia, Hospital Arnau de Vilanova, Lleida, Spain;
Ana Wägner, Hospital Universitario Insular de Gran Canaria, Spain;
Corrado Cilio, Malmö University Hospital, Malmö, Sweden;
Marc Donath (PI) and Patrizia Zala, University of Zurich, Zurich, Switzerland.

References

1. Mandrup-Poulsen T. The role of interleukin-1 in the pathogenesis of IDDM. *Diabetologia* 1996; **39**: 1005–1029.
2. Singh VK, Mehrotra S, Agarwal SS. The paradigm of Th1 and Th2 cytokines. *Immunol Res* 1999; **20**: 147–161.
3. Dinarello CA, Wolff SM. The role of interleukin-1 in disease. *N Engl J Med* 1993; **328**: 106–113. correction in 328: 744.
4. Dinarello CA. The many worlds of reducing interleukin-1. *Arthritis Rheum* 2005; **52**: 1960–1967.
5. Smeets RL, Joosten LAB, Arntz OJ, *et al*. Soluble interleukin-1 receptor accessory protein ameliorates collagen-induced arthritis by a different mode of action from that of interleukin-1 receptor antagonist. *Arthritis Rheum* 2005; **52**: 2202–2211.
6. 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.
7. Fleischmann RM, Tesser J, Schiff MH, *et al*. Safety of extended treatment with anakinra in patients with rheumatoid arthritis. *Ann Rheum Dis* 2006; **65**: 1006–1012.
8. Schiff MH, Divittorio G, Fleischmann RM, *et al*. The safety of anakinra in high-risk patients with active rheumatoid arthritis – six-month observations of patients with comorbid conditions. *Arthritis Rheum* 2004; **50**(6): 1752–1760.
9. Bendtzen K, Mandrup-Poulsen T, Nerup J, Nielsen JH, Dinarello CA, Svenson M. Cytotoxicity of human pI 7 interleukin-1 for pancreatic islets of Langerhans. *Science* 1986; **232**: 1545–1547.
10. Mandrup-Poulsen T, Bendtzen K, Nerup J, Dinarello CA, Svenson M, Nielsen JH. Affinity-purified human interleukin I is cytotoxic to isolated islets of Langerhans. *Diabetologia* 1986; **29**: 63–67.
11. Mathis D, Vence L, Benoist C. Beta-cell death during progression to diabetes. *Nature* 2001; **414**: 792–798.
12. Eizirik DL, Mandrup-Poulsen T. A choice of death – the signal-transduction of immune-mediated beta-cell apoptosis. *Diabetologia* 2001; **44**: 2115–2133.
13. Pascual V, Allantaz F, Arce E, *et al*. Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade. *J Exp Med* 2005; **201**(9): 1479–1486.
14. Hawkins PN, Lachmann HJ, Aganna E, McDermott MF. Spectrum of clinical features in Muckle-Wells syndrome and response to anakinra. *Arthritis Rheum* 2004; **50**(2): 607–612.
15. Hannum CH, Wilcox CJ, Arend WP, *et al*. Interleukin-1 receptor antagonist activity of a human interleukin-1 inhibitor. *Nature* 1990; **343**: 336–340.
16. Nuki G, Bresnihan B, Bear MB, McCabe D for the European Group of Clinical Investigators 2002; Long-term safety and maintenance of clinical improvement following treatment with anakinra (recombinant human interleukin-1 receptor antagonist) in patients with rheumatoid arthritis. *Arthritis Rheum* **46**(11): 2838–2846.
17. Palmer JP, Fleming GA, Greenbaum CJ, *et al*. C-peptide is the appropriate outcome measure for type 1 diabetes clinical trials to preserve beta-cell function: report of an ADA workshop, 21–22 October 2001. *Diabetes* 2004; **53**: 250–264.
18. Anti-inflammatory therapy with anakinra in newly diagnosed type 1 diabetes. Information provided by University of Texas Southwestern Medical Center, principal investigator: Soumya Adhikani, MD. www.Clinicaltrials.gov. 2009.
19. Safety and pharmacokinetics study of XOMA 052 in subjects with type 2 diabetes mellitus. Information provided by XOMA(US)LLC, study director: Alan M. Solinger, MD. www.Clinicaltrials.gov. 2009.
20. XOMA Ltd. XOMA 052 clinical results support new type 2 diabetes therapeutic approach of targeting inflammatory damage to insulin-producing cells. http://investors.xoma.com/releasedetail.cTm?releaseid=332743. 2008.

DOI: 10.1002/dmrr