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MONOGRAPH

XOMA-052

Humanized Anti-IL-1β Monoclonal Antibody
Treatment of Diabetes
Treatment of Rheumatoid Arthritis
Treatment of Cardiovascular Disorders

AB7
XMA-005.2

Humanized IgG_2 monoclonal antibody against human interleukin-1β

EN: 412018

SUMMARY

XOMA-052 is a humanized monoclonal antibody specific for human interleukin-1 (IL-1β) currently in phase II clinical trials in both Europe and the U.S. for the treatment of type 2 diabetes. Type 2 diabetes is an adult-onset metabolic disease strongly linked to diet and exercise, and is reaching epidemic proportions in both North America and Europe. XOMA-052 is believed to interrupt the inflammatory pathway mediated by the cytokine IL-1β via the IL-1 receptor. Molecular analysis has indicated a strong link between chronic inflammation and insulin resistance. Numerous inflammatory pathways are elevated in association with insulin regulation, but much research interest has focused on IL-1β, with the discovery that it is elevated in patients with type 2 diabetes, as well as those identified as having a high risk for developing the disease. As IL-1 receptors can be found on all nucleated cells, there is, by extension, potential for XOMA-052 to disrupt inflammatory responses in other diseases, such as rheumatoid and juvenile idiopathic arthritis, cardiovascular disorders and gout.

BACKGROUND

Interleukin-1β (IL-1β) is a potent regulator of the body's inflammatory response to assaults such as injury, infection and even antigenic challenge (1). IL-1β is primarily produced by macrophages, but an extremely wide variety of tissues, including epidermal, epithelial, lymphoid and vascular tissues, have been reported to synthesize IL-1β as well (2). With specific reference to metabolic diseases, IL-1β is secreted within the pancreatic islets, where insulin-producing β-cells are located. Detailed molecular analyses have linked a multitude of proteins to the failure of β-cells in the pancreas to produce sufficient amounts of insulin in insulin-responsive cells in order to maintain normoglycemia (1).

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IL-1β is produced in response to high glucose concentrations, which leads to decreased β-cell proliferation, loss of function and apoptosis (3). Unfortunately, inflammatory responses such as those involving IL-1β negatively affect pancreatic β-cell insulin secretion (4). As β-cells are one keystone in the regulation of normoglycemia, IL-1β-mediated destruction is potentially linked to the progression of insulin resistance, obesity and type 2 diabetes (5). Type 2 diabetes occurs when the β-cells of the pancreas are unable to function as part of the natural hormonal regulatory system in maintaining normal blood glucose levels (normoglycemia). Insufficient insulin levels result from both impaired β-cell function and reduced β-cell mass, and are often associated with system-wide insulin resistance. Therefore, effective therapies capable of preventing the multitude of mechanisms of β-cell failure are highly desirable (6).

There is considerable evidence indicating that obesity and insulin resistance are linked to chronic inflammation (7-11). Biomedical researchers have investigated a wide panel of inflammatory molecules and pathways, many of which have been associated with insulin, such as TNF-α, interleukin-6 (IL-6), nuclear factor NF-kappa-B (NF-κB) and IL-1β (5). Of the numerous cytokines and chemokines involved in the inflammatory response, interest in IL-1β followed the discovery that IL-1β was elevated in patients with type 2 diabetes, as well as those identified as having an increased risk of developing the disease (12-14). Briefly, IL-1β functions by binding to its cognate receptor, IL-1 receptor type 1 (IL-1RI), found on all nucleated cells and at high levels on pancreatic islets (15). Typical protein signaling complexes follow binding. Furthermore, the natural inhibitor, IL-1 receptor antagonist (IL-1ra), binds IL-1RI, preventing the recruitment of signaling complex proteins.

The naturally occurring antagonist of IL-1β, IL-1ra, has been shown to play a crucial role in preventing the pathogenesis of diabetes in cell culture models by both protecting β-cell function and reducing β-cell apoptosis (16). The hypothesis that using any means to block IL-1β will inhibit disease is further supported by data from a clinical trial indicating that IL-1ra treatment improved β-cell secretory function in patients with type 2 diabetes (17). Finally, it is also known that blocking IL-1β with specific anti-IL-1β monoclonal antibodies (mAbs)

can reduce cytotoxicity in response to inflammation (18), thus setting the stage for designing anti-inflammatory therapies (2, 19).

XOMA-052 is a human engineered $IgG_{2\kappa}$ antibody with a 97% human sequence and affinity for the cytokine IL-1β (20). Through its ability to bind IL-1β and block binding to the IL-1 receptor, XOMA-052 acts to inhibit the inflammatory response (Fig. 1). It is currently in phase II clinical trials in both Europe and the U.S. for the treatment of type 1 and type 2 diabetes. The promise of XOMA-052 is also being investigated in clinical trials in rheumatoid arthritis and Behçet's disease, and a clinical trial in cardiovascular disorders is planned. As testing moves forward in the developmental pipeline for the treatment of these clinically challenging diseases, a discussion of the potential of anti-inflammatory therapies (with a focus on mAbs used as a therapeutic specific for cytokine mediators of the disease process) is opportune (21). The obvious and unavoidable conundrum drug designers must compensate for in any anti-cytokine-based therapy developed for the treatment of chronic disease is that cytokines provide a survival benefit for the host via the innate immune response and are therefore an essential part of the first line of defense against infection and injury (2, 19). It is therefore unlikely that a treatment designed to completely block the bioactivity of any individual cytokine will lack serious side effects. As the obvious and effective type 2 diabetes treatment options involving diet and exercise are not associated with high levels of compliance among the ever-increasing numbers of patients with type 2 diabetes, additional therapeutic options are needed. The key to any mAb therapy designed for therapeutic antagonism of cellular signaling pathways will be the maintenance of important homeostatic signaling in biologically important pathways (22).

PRECLINICAL PHARMACOLOGY

Kinetic studies testing antibody modulation of receptor–ligand interactions have demonstrated that XOMA-052 has the ability to act as a potent inhibitor of IL-1β activity by reducing the affinity of IL-1β for its signaling receptor and coreceptor, but not for its decoy and soluble inhibitory receptors (22). Therefore, XOMA-052 has the ability to neutralize excess IL-1β while potentially allowing continued beneficial signaling in response to local inflammatory stimuli. Herein lies an intriguing potential for regulatory antibodies in therapy, and this line of investigation is well worth future monitoring.

In a diet-induced obesity (DIO) model of metabolic disease, XOMA-052 prevented mice exposed to a high-fat diet from experiencing increases in impaired glucose tolerance, insulin secretion and lipids, as well as β-cell apoptosis and proliferation, all pathologies observed in control mAb-treated mice (23). Additional analysis of fasting insulin and glucose levels in mice fed a high-fat diet but treated with either XOMA-052 or control mAb suggested that XOMA-052 also reduced high-fat diet-induced insulin sensitivity.

XOMA has recently expanded its development strategy for XOMA-052 to include investigations on the effects of treatment with this anti-IL-1β mAb on the reduction of cholesterol, plaque formation and damage to heart muscle, in an attempt to determine the potential for XOMA-052 in the treatment of cardiovascular diseases.

SAFETY

Phase I clinical trials have shown no serious adverse events in XOMA-052-treated patients with type 2 diabetes. Specifically, no serious infections were reported, no reports of drug-related hypoglycemia and no evidence of neutropenia. At the site of s.c. injection there were only mild reactions, similar to in placebo-treated patients. No significant changes in blood urea nitrogen (BUN) levels (an indicator of potential kidney malfunction) or transaminases (AST/ALT; the most sensitive indicators of liver cell irritation or damage) were reported. Patients did not experience significant changes in weight during the study. Of critical importance, there was no evidence of either immunogenicity to the therapy, nor the emergence of neutralizing antibodies over the course of the 84-day trial (24).

CLINICAL STUDIES

Two single-dose, placebo-controlled, dose-escalating phase I trials were performed in the U.S. and Switzerland in patients with type 2 diabetes. Thirty patients received single i.v. doses of 0.01, 0.03 or 0.1 mg/kg XOMA-052 and 9 received placebo and were followed for 56 days in the U.S. and 91 days in Switzerland. Sustained reductions in high-sensitivity C-reactive protein (hsCRP) of 20-49% were seen, as well as in glycosylated hemoglobin (HbA1c; up to 0.6%), with no evidence of suppressive effects on cytokines such as interferon α and IL-1ra (24, 25).

Further randomized, placebo-controlled phase I studies evaluated single and multiple s.c. doses of XOMA-052 of 0.03-0.3 mg/kg in patients with type 2 diabetes. Multiple doses were associated with clinically meaningful reductions in HbA1c (up to 0.6% at 0.03 mg/kg) and hsCRP (> 50% at 0.03 mg/kg) compared to single doses, with sustained improvements in fasting blood glucose and biomarkers of inflammation and cardiovascular risk (26, 27).

Finally, an open-label pilot study in patients with Behçet's disease who developed posterior panuveitis or retinal vasculitis despite ciclosporin and/or azathioprine treatment showed that treatment with a single i.v. infusion of 0.3 mg/kg XOMA-052 resulted in a rapid reduction in intraocular inflammation and improvement in visual acuity or other ophthalmic measures in all 7 patients, with no adverse events (28, 29).

XOMA-052 is also undergoing phase IIa (80 patients) and IIb (325 patients) clinical trials in patients with type 2 diabetes and a phase II trial in patients with type 1 diabetes, and a phase II trial in patients with cardiovascular disease is planned (30-33). A phase IIa clinical trial in patients with rheumatoid arthritis was initiated in 2009, but results have not been reported (34).

CONCLUSIONS

Type 2 diabetes is well on its way to becoming a worldwide epidemic, and as such, novel therapeutic strategies for dealing with this major health problem are of great interest and warrant continued monitoring as drugs go through clinical testing. Of course, as with any long-term therapy, the immunological safety of an mAb treatment has yet to be established. And finally, as basic biomedical researchers continue to investigate the autoimmune versus inflammatory contributions to diabetes, the ideal and optimal disease target for long-term treatment may yet be up for debate.

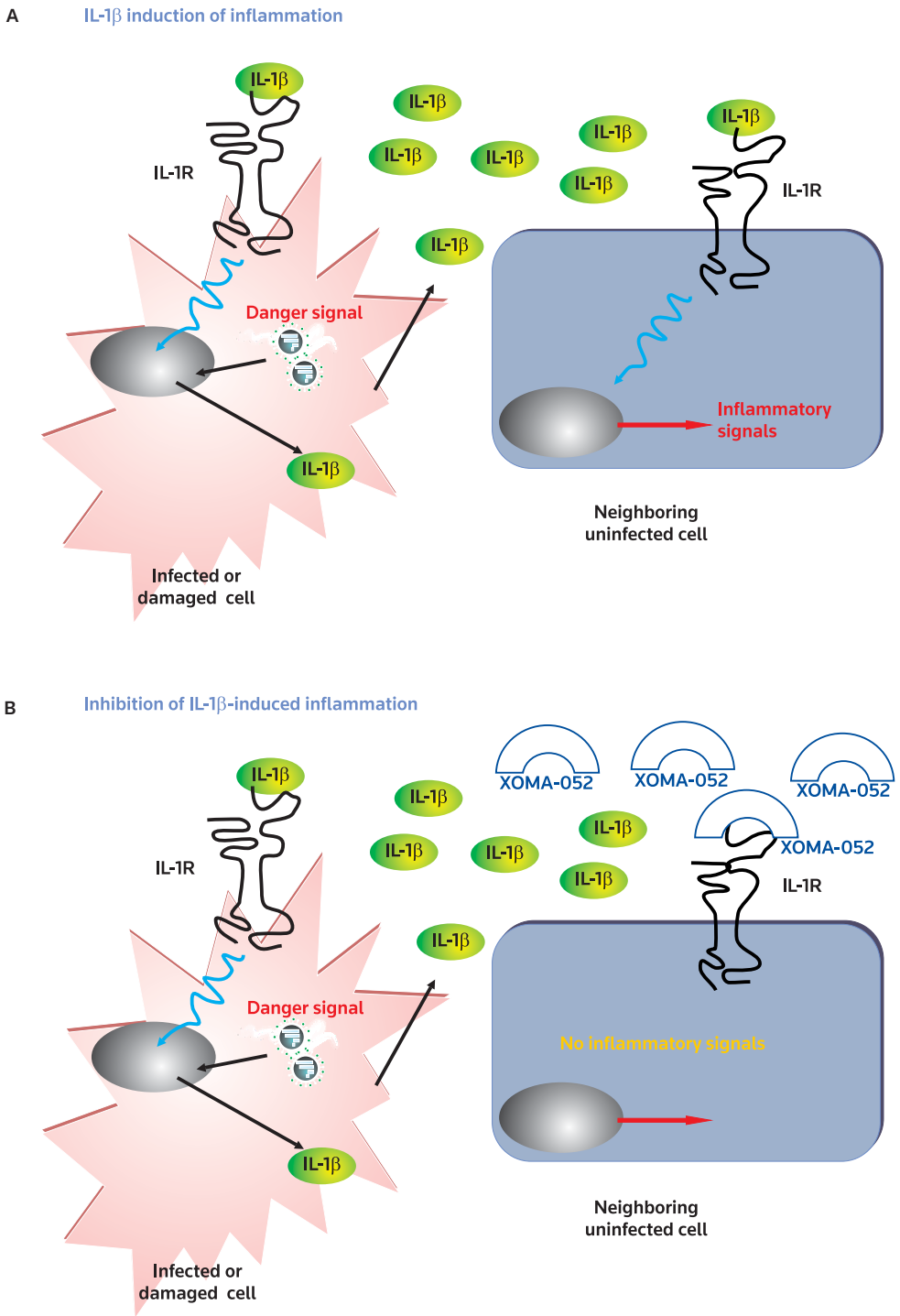

Figure 1. Schematic representation of the mechanism of XOMA-052 inhibition of IL-1β-induced inflammation. IL-1β is activated as a result of pathogen infection and/or tissue damage and acts by inducing and amplifying inflammation signals in adjacent cells and immune cells (**A**). XOMA-052 specifically blocks the IL-1β receptor, inhibiting IL-1β binding and the activation of the inflammatory signaling pathways (**B**).

SOURCE

XOMA, Ltd. (US).

DISCLOSURES

The authors state no conflicts of interest. Neither author has any association with XOMA or any other pharmaceutical company.

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