Drugs of the Future 2011, 36(6): 441-445

CCC: 0377-8282/2011
DOI: 10.1358/dof.2011.36.6.1598231

MONOGRAPH

SECUKINUMAB

Fully Human Anti-IL-17 Monoclonal Antibody

Prop INN; USAN

AIN-457
KB-03303A
NVP-AIN-457

Human monoclonal $IgG_{1\kappa}$ antibody against IL-17A

Immunoglobulin G_1, anti-(human interleukin-17A (IL-17, cytotoxic T-lymphocyte-associated antigen 8)); human monoclonal AIN457 γ1 heavy chain (230-215')-disulfide with human monoclonal AIN457 κ light chain dimer (236-236'':239-239'')-bisdisulfide

EN: 418942

SUMMARY

Secukinumab (AIN-457) is a fully human monoclonal antibody that neutralizes IL-17, thus affecting the immune response driven by Th17 lymphocytes. The Th17 response has been described to contribute to the inflammatory reaction seen in multiple immune-mediated diseases. Moreover, studies in animal models of autoimmune disease have proven the biological effects of the blockade of IL-17. Mostly, a decrease in the clinical signs and progression of certain immune-mediated diseases was noted. Recently, the results of the use of secukinumab in patients with psoriasis, rheumatoid arthritis, noninfectious uveitis and ankylosing spondylitis have been encouraging. Anti-IL-17 therapy may therefore offer a new therapeutic strategy for patients with immune-mediated diseases.

PREPARATION*

Transgenic female mice 27340 (Medarex, Inc.) in which the immunoglobulin variable and constant part genes are replaced by their human counterparts, are immunized with recombinant human IL-17 coupled to keyhole limpet hemocyanin (KLH). After immunization, mice are killed and their splenocytes are fused with myeloma PAI-0 cells using PEG 4000. Then, fused cells are grown and supernatants are collected and screened for antibody production, and clone 340-110-28 is selected. Finally, the culture supernatant from clone 340-110-28 is adjusted to pH 7.3 and loaded onto a Protein A Sepharose 4 fast flow column (Pharmacia), obtaining purified secukinumab (1).

BACKGROUND

The adaptive immune response comprises complex effector responses mediated by different subsets of T lymphocytes. In the presence of specific cytokines, the immune response polarizes to either a Th1 or Th2 helper T lymphocyte profile. The Th1 response is promoted and amplified by interferon-γ and IL-12; conversely, IL-4 triggers and enhances a Th2 response (2, 3). The Th1/Th2 cytokine profiles are antagonists and are essential for the differentiation into the helper T subsets. Recently, another lineage of helper T lymphocytes was described by three independent research groups. While studying the role of transforming growth factor-β (TGF-β) in the development of regulatory forkhead box protein P3+ T lymphocytes and its inhibition by IL-6, these groups found that their combination drove a shift to a new class of helper T lymphocytes (4-6). The combination of TGF-β plus IL-6 stimulates naive $CD4^+$ T lymphocytes to secrete IL-17 (3). This subset of Th17 lymphocytes differs in cytokine profile and biological effects from those of the Th1 and Th2 responses. IL-21 appears to be required for the development and autocrine amplification of the Th17 lineage, as does IL-23 (7-9). IL-17, a homodimeric molecule derived from activated Th17 cells, was identified by Rouvier et al. from a cDNA library (10, 11). Yao et al. were the first to describe the proinflammatory properties of IL-17A (12). To date, six different interleukins have been recognized as part of the IL-17 family, i.e., IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F (10, 13). IL-17A and IL-17F share 50% amino acid identity and are secreted by Th17 lymphocytes (10, 14, 15). Moreover, these interleukins may be secreted as disulfide homodimers (A/A, F/F) or as a heterodimer (A/F). These dimers may have overlapping biological functions but differ in their potency to induce an effect on their target cells (IL-17A > IL-17A/F > IL-17F) (10, 14-17). IL-17A is produced not only by Th17 lymphocytes, but also by macrophages, astrocytes, Langerhans cells and mast cells (13, 18-20). The Th17 response is systemic, as the receptors for IL-17A and IL-17F are ubiquitously expressed on fibroblasts, keratinocytes, macrophages, dendritic cells, endothelial cells, epithelial cells, chondrocytes and osteoblasts (21, 22).

The IL-17 receptor family includes IL-17RA, IL-17RB, IL-17RC, IL-17RD and IL-17RE. Of these, IL-17RA and IL-17RC are the most studied, as they are specific for both IL-17A and IL-17F (3, 13, 21, 22). Although the biochemical structure and interactions of this receptor family have been elucidated, the downstream cascade of the IL-17R complexes is still not known in detail (3).

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The IL-17/Th17 response may be defined as the arm of adaptive immunity associated with the clearance of pathogens that are not adequately handled by the Th1 or Th2 immune responses; it elicits massive inflammation, marked predominantly by neutrophil infiltration. A myriad of pathogens may trigger the Th17 response, including Gram-positive (*Propionibacterium acnes, Staphylococcus aureus*), Gram-negative (*Citrobacter rodentium, Klebsiella pneumoniae, Borrelia burgdorferi, Bacteroides* spp.), acid-fast (*Mycobacterium tuberculosis*) and fungi-like (*Pneumocystis carinii*) microorganisms (3, 7, 10). Inflammatory responses against fungal infections have also been linked to the Th17 subset of helper T cells, especially *Candida albicans* (23, 24). There is evidence that supports the activation of the Th17/IL-17 response in human psoriasis (13, 25, 26), atopic dermatitis (27), rheumatoid arthritis (13, 18, 28, 29), uveitis (13, 30), multiple sclerosis (19, 31), inflammatory bowel disease (32) and asthma (20).

The Th17 immune response and its role in human immune-mediated diseases have been studied over the last decade. Hamzaoui et al. reported the cytokine profile observed in patients with Adamantiades-Behçet disease (ABD) (33). Proinflammatory cytokine IL-17A serum levels were higher in patients with ABD than in healthy individuals, independent of the disease activity. Moreover, patients with active disease had increased IL-17 levels compared to patients in remission, which suggests the IL-17 serum level as a possible indicator of ABD activity. Multiple studies had proven the contribution of Th17 lymphocytes to autoimmune disease in either rodents or humans; however, Adami-Obi et al. firmly validated the occurrence of a Th17 lymphocyte response in human uveitis and scleritis in a rodent model of experimental autoimmune uveitis (EAU). IL-17 was found to be normally expressed in the peripheral blood mononuclear cells (PBMCs) of healthy subjects and patients with inactive disease, and it was significantly elevated in patients with active uveitis or scleritis. Moreover, treatment with specific anti-IL-17 antibodies significantly decreased inflammation in EAU rodents. The results confirmed that the severity of inflammation may be decreased by blocking the IL-17 response with a specific antibody (34).

Numerous studies have been performed to understand the biological effects of blocking the Th17 response in animal models of inflammation and autoimmunity (35). These efforts include experimental anti-IL-17A antibodies and selective anti-IL-17A RNA aptamers. Chao et al. studied the effects of anti-IL-17A antibody injection in experimental animal models of rheumatoid arthritis (36). Using the rat adjuvant-induced arthritis (rAIA) and the mouse collagen-induced arthritis (mCIA) models, they demonstrated efficacy in preventing inflammation and bone erosion for the anti-IL-17A antibody compared to placebo. Subcutaneous injection of anti-IL-17A antibodies in rAIA models with established severe arthritis significantly reduced and reversed bone erosion measured by X-ray analysis. A decrease in arthritis-elevated and osteoclast-specific gene expression was also documented. In addition, s.c. injection of the anti-IL-17A antibody in mCIA models proved to delay and reduce the incidence of arthritis in these models. Moreover, anti-IL-17 antibody treatment of mice with established arthritis prevented the development of inflammation in the unaffected paws.

The therapeutic effect of IL-17A neutralization has also been studied in the murine autoimmune encephalomyelitis (EAE) model of multiple sclerosis. Hofstetter et al. proved that IL-17-producing T lymphocytes are present in the murine EAE model; additionally, IL-17 was detected both in the spleen, representing the peripheral induction phase of EAE, and in the central nervous system (target organ), representing the local autoimmune T-lymphocyte response (37). Two strategies were used to assess the efficacy of blocking the IL-17 response. First, the neutralization with an IL-17 receptor-Fc fusion protein during the ongoing acute EAE resulted in a significant improvement in clinical symptoms. Additionally, neutralization with the MAb as prophylactic therapy reduced the severity of EAE compared with placebo.

The role of Th17 lymphocytes in triggering and maintaining the inflammatory response in ocular inflammation has also been studied in experimental autoimmune uveoretinitis (EAU). The use of specific anti-IL-17 antibodies proved to be effective in reducing the severity of inflammation in experimental uveitis (34). Interestingly, the involvement of Th17 lymphocytes in uveitis apparently occurs in the late phases of the disease, and possibly does not contribute to the early stages of EAU. Yoshimura et al. confirmed that Th1 lymphocytes are required for inducing EAU, while Th17 lymphocytes contribute to sustaining the inflammatory response in the late phases of EAU (38). The exact role and interactions of the Th1/Th17 cytokine profiles in acute and chronic inflammation remain to be elucidated. However, the results of blocking IL-17A in patients with chronic immune-mediated diseases are promising, which supports the possible role of Th17 lymphocytes in sustaining chronic inflammation.

The use of IL-17A antagonist antibodies has also been studied in murine models of allergen-induced airways inflammation. Injection of an anti-IL-17A antibody to ovalbumin-inhaled mice during the challenge phase with antigen reduced the airways inflammation, eosinophilic infiltration and hyperresponsiveness (39). The role of IL-17 in allergen-induced inflammation and the potential benefit of anti-IL-17 therapy in asthma and chronic obstructive pulmonary disease (COPD) are not clearly understood.

Recently, Ishiguro et al. explored the potential effects of an RNA aptamer directed against human IL-17A in mouse autoimmunity models (35). After the selection and amplification of the human IL-17A aptamer was done, the affinity for the human and mouse IL-17A receptor was measured. The aptamer against human IL-17A was effective in inhibiting inflammatory lesions and neurological symptoms in the rheumatoid arthritis and EAE mouse models. These results provide an alternative promising therapeutic approach to autoimmune disease. Aptamers appear to have greater affinity for IL-17A than monoclonal anti-IL-17A antibodies, although they need to be modified chemically to improve their pharmacokinetic properties, such as their half-life (35, 40).

The therapeutic effects of the blockade of IL-17A in animal models provide a promising panorama of future therapies in human disease. The large number of diseases in which IL-17A possibly promotes and sustains inflammation is impressive; therefore, the development of specific antibodies and aptamers that target the Th17 immune response, especially IL-17A and/or IL-17 receptors, is of utmost relevance.

MAbs have become available over the last decade for the treatment of solid and hematological cancers and for immune-mediated diseases. To date, there are 19 FDA-approved MAbs for the treatment of different diseases and it is estimated that about 150 MAbs are currently in clinical development (41, 42). MAbs are usually adminis-

tered intravenously (i.v.), intramuscularly (i.m.) or subcutaneously (s.c.) and may be engineered to target specific molecules.

PRECLINICAL PHARMACOLOGY

Secukinumab (AIN-457) is a novel, highly specific human immunoglobulin $G_{1\kappa}$ ($IgG_{1\kappa}$) MAb that binds and neutralizes human IL-17 and blocks the IL-17A pathway (13, 40). The efficacy and safety of secukinumab have been studied in patients with psoriasis, rheumatoid arthritis, chronic noninfectious uveitis and ankylosing spondylitis.

PHARMACOKINETICS AND METABOLISM

MAbs have special pharmacokinetics, with long half-lives observed for most of them. Although this makes it difficult to establish the best dosing regimen for each MAb, it also allows for a reduced administration frequency (41). IgG is the most common antibody class chosen when developing a new MAb, given its longer half-life (21 days) (43). The IgG_3 subclass is the exception to this, as it has a much shorter half-life (7 days). Given their relatively large size, MAbs usually have a very limited ability to distribute from the blood compartment into the peripheral tissues. Metabolism and elimination typically involve proteolysis, target-mediated elimination and nonspecific endocytosis. Of importance is the formation of antibodies against MAbs, which may affect their efficacy by accelerating their clearance (41).

SAFETY

Recently, Hueber et al. reported the safety and efficacy of secukinumab in patients with chronic plaque psoriasis, rheumatoid arthritis and noninfectious uveitis (13). A total of 104 patients were enrolled in 3 different clinical trials to evaluate the effect of i.v. anti-IL-17 antibody therapy at doses of 3-10 mg/kg. Patients were randomized to receive either the drug or placebo, and safety was assessed in both groups. Overall, as with other available MAbs, secukinumab proved to be safe for humans, with no deaths reported in the clinical trials. Moreover, immunogenicity to the fully human MAb was not detected. The incidence of severe adverse events (SAEs) and adverse events (AEs) was fairly similar in the secukinumab and placebo groups in the three clinical trials. One patient in the psoriasis trial developed an SAE; no differences in AE incidence rates were found between secukinumab and placebo groups. None of the patients discontinued therapy due to AEs or SAEs. Three patients in the rheumatoid arthritis trial developed SAEs, one in the secukinumab group and two in the placebo group. The AE incidence rate was slightly higher in the secukinumab group. Infections were reported as nonserious and occurring at the same rate in both groups. Worsening of arthritis was observed equally in both groups. In the uveitis trial, no SAEs were reported; AEs were experienced in 63% of the patients. The most frequent AEs reported were headache (56%), upper abdominal pain (19%) and conjunctival hyperemia (19%).

More recently, Baeten et al. reported preliminary results on the safety and efficacy of secukinumab in the treatment of ankylosing spondylitis (45). Thirty patients with active ankylosing spondylitis were enrolled in a double-blind, placebo-controlled study. Patients in the treatment group received two infusions of secukinumab 10 mg/kg. So far, two SAEs have been recorded: one case of hypertension and another of subcutaneous abscess requiring drainage. However, as the double-blind safety analysis is still ongoing, data cannot be unblinded as yet. Overall, the frequency of adverse events was not different from that observed by Hueber et al. (13). To date, secukinumab has shown a good safety profile, similar to other fully human antibodies. However, more studies to assess the safety and tolerability in humans are currently being conducted.

The results of a phase IIb trial of the use of secukinumab in patients with rheumatoid arthritis have recently been published (46). Two hundred and thirty-seven patients with rheumatoid arthritis on methotrexate were randomized to receive monthly s.c. injections of secukinumab of 25, 75, 150 and 300 mg, or placebo. Secukinumab showed a safe profile after 20 weeks of follow-up, comparable to placebo. None of the patients needed to discontinue therapy due to AEs. SAEs were reported in six patients, most of them in the group receiving secukinumab 300 mg; the relevance of this remains to be clarified.

CLINICAL STUDIES

In addition to reporting on its safety profile, Hueber et al. also documented the efficacy of secukinumab in patients with chronic plaque psoriasis, rheumatoid arthritis and noninfectious uveitis (13). The response to secukinumab in patients with active psoriasis was assessed by measuring the Psoriasis Area and Severity Index (PASI). Thirty-six patients were randomized to receive a single infusion of secukinumab 3 mg/kg or placebo and reassessed at 12 weeks. A total of 75% of patients on secukinumab achieved a clinically meaningful reduction of inflammation; moreover, the clinical response was associated with a reduction in the histomorphological signs of acanthosis and epidermal hyperplasia. An expected decrease in the expression of IL-17A and IL-22 was also noted. The first-in-human trial of secukinumab in patients with rheumatoid arthritis was designed to assess the safety, tolerability and pharmacokinetics of single or multiple doses. The efficacy in the cohort of patients who received two infusions of secukinumab (10 mg/kg) or placebo was reported. The interval between infusions was set at 3 weeks considering the expected half-life of 3-4 weeks. The response to secukinumab in patients with rheumatoid arthritis was assessed by measuring the American College of Rheumatology 20% response score (ACR20), the 28-joint disease activity score (DAS28) and the C-reactive protein serum levels. The area under the time–response curve was significantly higher for the secukinumab group than for placebo. Moreover, clinical improvement was noted to occur rapidly and to be maintained for up to 13 weeks after the second infusion. These results suggest a potential benefit in suppressing synovial inflammation in patients with active rheumatoid arthritis. The assessment of tolerability and pharmacokinetics is currently ongoing. The uveitis trial was designed as an open-label study to enroll patients with active uveitis who required systemic immunosuppressive therapy to receive two infusions of secukinumab 10 mg/kg. Efficacy was measured by clinical response (i.e., improvement in visual acuity, reduction in ocular inflammation) or the ability to stop corticosteroid therapy. The results were compared to the reported efficacy of infliximab therapy for refractory uveitis. Secukinumab was shown to be as effective as infliximab for treating refractory uveitis,

rapidly achieving a sustained reduction in vitreous haze and an improvement in visual acuity. These results suggest that secukinumab may be beneficial in severe, chronic noninfectious uveitis that requires systemic immunosuppressive therapy.

The efficacy of secukinumab has also been assessed in patients with ankylosing spondylitis (45). The primary endpoint was to measure the proportion of patients achieving the Assessment of Spondylo-Arthritis International Society (ASAS) 20 response at week 6. Secukinumab proved to be effective in rapidly inducing inflammatory control in 23 of the 24 patients with ankylosing spondylitis receiving the medication. This was statistically significant when compared to the placebo group.

In addition, Genovese et al. demonstrated the effectiveness of secukinumab in inducing responses in patients with rheumatoid arthritis receiving doses of 75, 150 and 300 mg compared to those receiving doses of 25 mg or placebo (46). These results were not statistically significant due to an unexplained increase in ACR20 in the placebo group during follow-up. However, there was a statistically significant reduction in clinical signs and symptoms measured by the DAS28 score in the 75-300 mg groups versus placebo. The effects of IL-17 blockade were sustained over 24 weeks.

Results on the efficacy of IL-17 response blockade in immune-mediated diseases are promising. Ongoing clinical trials are assessing the efficacy, tolerability, pharmacokinetics and safety profile in patients with immunological disorders.

SOURCE

Novartis AG (DE).

DISCLOSURES

The authors state no conflicts of interest.

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