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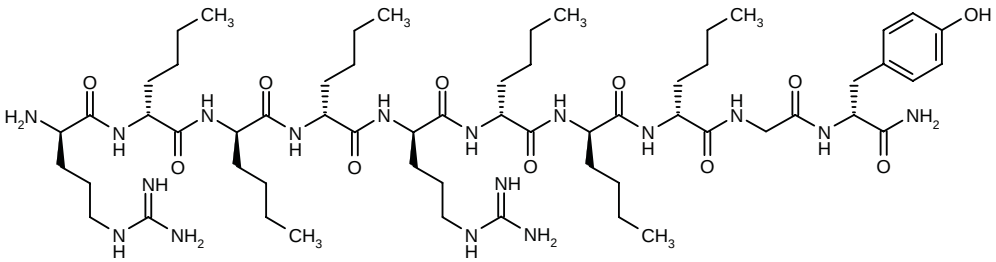
RDP-58

Treatment of Inflammatory Bowel Disease
TNF-α Production Inhibitor

Allotrap-1258

H-D-Arg-D-Nle-D-Nle-D-Nle-D-Arg-D-Nle-D-Nle-D-Nle-Gly-D-Tyr-NH_2



$C_{59}H_{105}N_{17}O$
Mol wt: 1228.587
CAS: 287096-87-1
EN: 278534

Abstract

Inflammatory bowel diseases (IBDs), of which Crohn's disease and ulcerative colitis are the most common, are chronic inflammatory disorders of the gastrointestinal (GI) tract that can lead to tissue damage and irreversible impairment of GI tract structure and function. The chronic mucosal inflammation evident in IBD results from immune dysfunction, where inappropriate T-cell responses to antigen and overexpression of proinflammatory cytokines play a central role. Tumor necrosis factor-α (TNF-α) in particular has been identified as a key mediator in these disorders, promoting chronic inflammation and tissue damage. In fact, anti-TNF monoclonal antibodies (MAbs) have shown efficacy in reducing IBD-associated inflammation and in promoting mucosal healing in the clinic. However, repeated systemic MAb administration is associated with complications Thus, the search continues for new agents to inhibit TNF expression. RDP-58 is a 10-amino-acid immunomodulating peptide derived from the heavy chain of an HLA class I molecule that was shown to block the p38 and JNK (c-Jun *N*-kinase) MAP (mitogen-activated protein) kinase pathways and potently inhibit TNF-α, interferon γ (IFN-γ) and IL-12 synthesis and upregulate heme oxygenase-1 (HO-1) enzyme activity. RDP-58 exhibited efficacy in several disease models and was chosen for further development.

Introduction

Inflammatory bowel diseases (IBDs) are chronic inflammatory disorders of the gastrointestinal (GI) tract and include Crohn's disease, ulcerative colitis, microscopic (or lymphocytic) colitis, diversion colitis, fulminant colitis and toxic megacolon. The chronic inflammation characteristic of these diseases can lead to tissue damage and long-term irreversible impairment of GI tract structure and function. Inflammatory bowel disease is a disorder that primarily affects Western populations, with a higher incidence noted in urbancompared to rural areas. The incidence of IBD has increased up to 6-fold in the past 25 years and it is estimated that up to 1 million Americans suffer from IBD (1, 2).

Crohn's disease and ulcerative colitis are the most common forms of IBD and are due to abnormal immune responses. Both types involve inflammation and ulceration of the intestines; however, in general, ulcerative colitis is limited to the rectum and colon, while Crohn's disease extends into the intestinal wall and can affect the entire digestive tract from the mouth to the anus. The cause of these disorders has not been elucidated, although it appears that genetic (*e.g.*, mutations in the gene encoding NOD2 are seen in some patients with Crohn's disease) and environmental factors, together with abnormal immune responses, play a crucial role in the pathogenesis of IBD (1, 2). The chronic mucosal inflammation present in ulcerative colitis and Crohn's disease is due to immunological defects which result in inappropriate T-cell responses to antigen and overexpression of proinflammatory cytokines such as the

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interleukins IL-1, IL-8, IL-6, IL-12 and IL-13, interferon γ (IFN-γ) and tumor necrosis factor-α (TNF-α) (3, 4). Several studies have identified TNF as a key mediator that promotes chronic inflammation and tissue damage, and clinical studies using anti-TNF monoclonal antibodies (MAbs; *e.g.*, infliximab, adalimumab) have demonstrated the efficacy of this treatment strategy in reducing inflammation and promoting mucosal healing (5-11). However, repeated systemic MAb administration can result in complications. Thus, the search continues for new agents to inhibit TNF expression.

Peptides derived from the heavy chain of HLA class I molecules have been shown to modulate immune responses both *in vitro* and *in vivo*. These peptides can inhibit the cytotoxicity and differentiation of cytotoxic T-cells (CTLs) *in vitro* and prolong allograft survival *in vivo* (12-14). Using a novel computer-assisted rational design approach based on peptide 2702.75-84 derived from HLA-B2702, the immunomodulatory 10-amino-acid peptide RDP-58 (Allotrap-1258) was identified. RDP-58 consists of 9 D-amino acids which are resistant to degradation by human protease enzymes and a glycine. RDP-58 is the D-isomer and the L-isomer (RDP-1258) exhibits similar biological activity, including potent inhibition of TNF synthesis and upregulation of heme oxygenase-1 (HO-1) activity (an indication of inhibition of inflammation). RDP-58 was chosen for further development as a treatment for IBD (15-17).

Pharmacological Actions

In *in vitro* experiments using mouse, rat or human cell lysates, addition of RDP-58 concentration-dependently inhibited HO-1 activity. However, treatment of mice and rats *in vivo* with the agent upregulated HO-1 mRNA at 6 h postdosing, with increased HO-1 protein levels detected at 24, 48 and 72 h. It was suggested that this upregulation, commonly seen with other HO inhibitors, is due to accumulation of heme following inhibition of HO activity (17).

Studies *in vitro* using murine (RAW264.7) and human (THP-1) macrophage cell lines showed that RDP-58 concentration-dependently inhibited lipopolysaccharide (LPS)- and LPS+IFN-γ-stimulated TNF production (IC_{50} = 20 μM). Results obtained *in vivo* showed that treatment of concanavalin A-challenged C57BL/6 mice with RDP-58 (5 mg/kg i.p.) decreased TNF plasma levels by 75% at 60 min postdosing; IFN-γ levels were reduced by 50% at 360 min postdosing with 5-50 mg/kg i.p. RDP-58. Levels of IL-1β, IL-2, IL-4, IL-6 and IL-10 were unaffected by treatment. RDP-58 also inhibited TNF production in C57BL/6, CBA, inducible nitric oxide synthase (iNOS) knockout and HO-1 knockout mice challenged with LPS or D-galactosamine (GalN), indicating that the effects of the agent were independent of iNOS or HO-1. Further experiments using mouse thioglycollate-elicited peritoneal macrophages (TEPM) isolated from transgenic Tg1278 (containing the human wild-type TNF-3'-untranslated region [UTR]) and Tg197 (containing a 3'-modified human TNF transgene bearing the 3'-UTR of the human β-globin gene) cell lines were performed to determine whether RDP-58-induced inhibition of TNF production was translational or posttranslational. Results indicated that the agent did not affect TNF mRNA steady-state levels, but instead inhibited protein synthesis. While deletion of the AU-rich element in the 3'-UTR of TNF mRNA had little effect on RDP-58-mediated inhibition of LPS-stimulated TNF production, the agent became inactive when the TNF 3'-UTR was replaced with the human globin 3'-UTR (TEMP Tg197 cells). These results suggest that the inhibitory activity of RDP-58 is dependent on elements in the 3'-UTR of TNF mRNA that have not yet been identified (18).

Further molecular studies showed that RDP-58 inhibits phosphorylation of p38 MAP (mitogen-activated protein) kinase and JNK (c-Jun *N*-kinase), which are involved in translational regulation of TNF-α mRNA stability and the upstream regulation of transcription factors mediating cytokine expression (19, 20).

Another *in vitro* study using mouse and human macrophage cell lines demonstrated that RDP-58 had minimal effects on LPS-stimulated nuclear TNF-α levels but significantly decreased cytoplasmic mRNA levels, suggesting that the agent inhibits TNF-α stability and/or nuclear export; RDP-58 also decreased total IL-12 mRNA levels. Nuclear but not cytoplasmic levels of IFN-γ were significantly decreased in IL-18+TNF-α-stimulated KG-1 cells treated with RDP-58, suggesting effects at both the transcriptional and translational levels. Experiments using several cell lines demonstrated that RDP-58 inhibited the phosphorylation of p38 MAP kinase and JNK1/JNK2 kinases, in addition to significantly reducing both NF-κB and AP-1 transcription factor binding (21).

An *in vivo* study using an Skh/hr hairless mouse skin model investigated the immunomodulatory effects of RDP-58. Administration of the agent (3 mg/g i.p.) 1 h before UVB light exposure (2240 J/m^2) significantly decreased UV-induced TNF-α production in the epidermis. RDP-58 (0.3, 1 or 3 mg/g i.p.) did not affect skin steady-state TNF-α mRNA levels at 48 h post-UV exposure. RDP-58 did not reduce dermal myeloperoxidase activity (MPO; *i.e.*, indicates the extent of neutrophil activation and a marker of acute UVB-induced inflammatory response) or cutaneous skin edema at 48 h post-UV exposure, suggesting that RDP-58 specifically blocks a component of UVB-induced acute inflammatory responses, such as TNF protein synthesis (22).

The potential efficacy of RDP-58 as a treatment for IBD was demonstrated in animal models of colitis. In experiments using C57BL/6 mice with dextran sodium sulfate (DSS)-induced colitis, oral administration of RDP-58 (5 mg/kg/day starting at the initiation of DSS treatment) markedly reduced the severity of colitis, including decreases in occult blood, gross bleeding and diarrhea, and preserved the intestinal mucosa (*i.e.*, architecture of colonic epithelium). Reduced but significant protection from colitis was also observed in animals

treated with RDP-58 at doses of 1 mg/kg/day p.o. and 5 mg/kg/day i.p. Treatment with RDP-58 was shown to partially reverse inhibition of colonic epithelial cell proliferation, completely reverse colonic epithelial cell death and inhibit the accumulation of neutrophils in the colon induced by DSS treatment. The expression of TNF was also downregulated (23).

Another study also using mice with DSS-induced colitis showed that treatment with RDP-58 (5 or 10 mg/kg/day p.o. for 8 days starting when DSS was stopped) significantly reduced disease activity indices (DAI) and histological scores as compared to controls and animals treated with aspirin (50 mg/kg/day). Animals treated with RDP-58 also exhibited significantly reduced acute, chronic and total inflammation scores and enhanced re-epithelialization, as indicated by a decrease in crypt scores (24).

The efficacy of RDP-58 in reducing mucosal injury was demonstrated in rats with colitis induced by rectal instillation of 2,4,6-trinitrobenzene sulfonic acid (TNBS)/ethanol. RDP-58 treatment significantly reduced weight loss, diarrhea, colonic inflammatory infiltrates and bowel wall thickness. Macroscopic necroses and microscopic ulcerations of rats treated with the agent (5 mg/kg/day p.o. from 3 days before and for 7 days after colitis induction) were significantly decreased by 47% and 41%, respectively, as compared to controls. RDP-58 had no protective effects, however, when administered only for 3 days prior to colitis induction. Differences in mucosal proliferation were not observed with RDP-58 treatment (25, 26).

In further experiments, RDP-58 was shown to inhibit TNF production *ex vivo* in human biopsy specimens and lamina propria mononuclear cells (LPMNCs) from inflamed colonic mucosa of patients with Crohn's disease. Incubation with the agent (50 μM for 24 h) resulted in reductions compared to untreated samples in TNF (6 pg/ml *vs.* 23 pg/ml in biopsies; 120 ± 30 pg/ml *vs.* 276 ± 63 pg/ml in LPMNCs) and IFN-γ (7 ± 3 pg/ml *vs.* 19 ± 7 pg/ml in LPMNCs). Examination of cytokine production in LPMNCs revealed that treatment with RDP-58 had no significant effect on TNF-α, IL-1β or IFN-γ mRNA levels (26).

A study in rhesus and cynomolgus monkeys with spontaneous colitis showed rapid (within 1 day of dosing) and prolonged (for up to 3 weeks postdosing) efficacy for oral RDP-58 (0.75, 1.3, 2 or 5.5 mg/kg p.o. 3 times/week for 3 weeks). RDP-58 was safe and improved stool quality and resolved diarrhea. Intravenous administration of RDP-58 (0.25 or 0.5 mg/kg as a single infusion or 0.5 mg/kg 3 times/week) was also effective in these animals. Treatment with the agent had no effect on blood cell parameters and metabolic profiles (27).

In addition to improving colitis, preclinical findings suggested potential for RDP-58 in other indications.

A study using a mouse bleomycin-induced fibrosis model demonstrated that a single intratracheal instillation of RDP-58 on day 0 significantly reduced leukocyte infiltration and TNF-α levels in bronchial lavage fluid on day 7. Subsequent fibrosis analyzed on day 28 was also inhibited by treatment. RDP-58 was also effective in inhibiting pulmonary inflammation and fibrosis when administered on day 7. These results suggest that RDP-58 may be effective in both treating and preventing lung fibrosis (28).

The efficacy of RDP-58 in preventing graft-*vs.*-host disease (GvHD) was examined in a study using an SCID-hu mouse model in which mice were implanted with human peripheral blood lymphocytes. Survival of mice treated for 2 weeks with RDP-58 (1 mg/kg/day i.p. 3 times/week) was prolonged 2.6-fold as compared to untreated controls (66 days *vs.* 25 days). Human TNF-α, IFN-γ levels and human immunoglobulin levels in treated animals measured at 3 days postimplantation were 57%, 47% and 63%, respectively, lower compared to untreated controls (29).

RDP-58 was also shown to inhibit chronic rejection in a study using C3H($H2^k$) mice bearing abdominal aorta transplants from C57BL/10 donors. Arteriosclerosis of aortic allografts was inhibited in animals treated with RDP-58 (0.1, 0.5 or 2.5 m/kg i.p. every other day. after transplantation) so that vascular intimal thickening and media necrosis were markedly inhibited on day 30 postimplantation; adventitial cellular inflammation was unaffected by treatment. It was speculated that the agent inhibits chronic rejection via direct effects on smooth muscle cells, since treatment of a rat smooth muscle cell line (A10) *in vitro* concentration-dependently inhibited proliferation (80% at 100 μM) and TNF-α-induced apoptosis (IC_{50} = 10 μM) (30).

Results from a mouse model of inflammatory cystitis showed that bladder instillation of RDP-58 (1 mg/ml for 30 min starting 45 min after LPS instillation) significantly reduced submucosal polymorphonuclear (PMN) and mast cell counts by 83% and 45%, respectively, and decreased edema by 70%. Results suggest that RDP-58 may be effective as a treatment for interstitial cystitis (31).

Other preclinical results suggest that RDP-58 may be effective in enhancing the efficacy of and reducing GI toxicity and mortality related to chemotherapeutic agents. RDP-58 has been shown to significantly decrease irinotecan- and 5-fluorouracil (5-FU)-induced diarrhea and mortality in mice. Treatment of CT-26 murine colon carcinoma-bearing mice with the maximum tolerated dose (MTD; 600 mg/kg) or 2 x MTD of irinotecan reduced tumor volume by about 40% and 85%, respectively, as compared to controls. Although 10-20% of the mice treated with irinotecan at 2 x MTD had complete responses (versus 0 in the group treated with 1 x MTD), a 50% mortality rate was observed. In contrast, 90-100% of the mice treated with a combination of irinotecan at 2 x MTD and oral RDP-58 survived. Mice treated with the combination also had a decrease in the incidence of diarrhea and in weight loss. Histological analysis revealed that RDP-58 treatment protected intestinal mucosa from irinotecan-induced epithelial apoptosis and morphological damage in both the villus and crypt compartments. Irinotecan-induced overproduction of intestinal TNF-α, IFN-γ and IL-12 was also prevented with RDP-58. Similar results

were obtained using mice bearing 4T1 murine mammary adenocarcinoma (32, 33).

Pharmacokinetics

The pharmacokinetics, bioavailability, tissue distribution and excretion of RDP-58 were examined in dogs, normal mice and mice with DSS-induced inflammation of the GI tract. Little or no systemic absorption was observed up to 72 h postdosing with [^{14}C]-labeled RDP-58 (10 or 100 mg/kg p.o.). Most of the radioactivity (85-100%) was detected in feces at 24 h postdosing. Following administration of an i.v. bolus (over 20 min) of the labeled drug to dogs, about 80% of the radioactivity was found in the liver within 24-96 h postdosing, suggesting hepatic accumulation with delayed elimination. Radioactivity following i.v. administration was eliminated mainly in the feces, indicating biliary excretion of systemically available RDP-58 (17, 24).

Toxicity

The toxicity of repeated-dose RDP-58 up to 50, 10 and 20 mg/kg/day for mice, dogs and monkeys, respectively, for 28 days with a 14-day recovery period was examined. No significant clinical effects were observed on hematology, clinical chemistry, body weight, urinalysis or food consumption in any species. No GI irritation (*i.e.*, lesions), alterations in gut-associated lymphoid tissue or gross or histopathological changes of any tissue were observed with repeated dosing. RDP-58 lacked immunogenicity in all species examined since no anti-RDP-58 antibodies were detected in plasma (17, 24).

Clinical Studies

RDP-58 was concluded to be safe in a phase I trial conducted in 24 healthy male volunteers who received a single oral dose (25, 100 or 300 mg) followed by daily dosing for 28 days. No significant changes in hematology, biochemistry or Q-Tc intervals were seen with treatment. Pre- and postdose hemoglobin, AST, ALP and creatinine levels were similar. Mild adverse events such as headache (24%), vomiting (12%) and nausea (5%) were seen in 85% of the volunteers and were less common in the group receiving the highest dose. One serious adverse event (myocardial infarction) was reported in a patient subsequently determined to have triple-vessel disease and concluded to be unrelated to RDP-58 treatment (34).

A multicenter, parallel, prospective, randomized, blinded, placebo-controlled phase II trial conducted in 127 patients with mild to moderate ulcerative colitis examined the efficacy of RDP-58 (100, 200 or 300 mg daily for 28 days). RDP-58 was well tolerated. Adverse events were similar in treatment and placebo groups. Three patients on placebo and 1 receiving the 100-mg RDP-58 dose experienced serious adverse events (*i.e.*, hospital admission for worsening colitis). At 28 days, the clinical remission rates for patients receiving the 200- and 300-mg doses were significantly higher than for the placebo and 100-mg RDP-58 groups, which were not significantly different (70%, 72%, 40% and 29%, respectively). Similarly, response rates for the higher dose groups were significantly greater than for placebo and the low-dose group, which again were not significantly different (77%, 72%, 44% and 33%, respectively). Histology scores were also significantly improved in the 200- and 300-mg groups as compared to placebo. During the treatment period, 13% of the patients worsened in the 200-mg RDP-58 group as compared to 30% on placebo (35, 36).

Results reported from a multicenter, randomized, blinded, placebo-controlled phase II trial in 104 patients with Crohn's disease (Crohn's Disease Activity Index [CDAI] = 220-400 at entry) indicated that further investigation is required to determine whether RDP-58 (100, 200 or 300 mg/day p.o. for 28 days) is effective in this indication. No significant differences were observed for response and remission rates between placebo and active treatment groups. Although 66% of the patients receiving a dose of 200 mg achieved a response, a mere 48% response rate was obtained in the highest dose group, which was not significantly different from the rates of 43% and 44% obtained in the placebo and 100-mg RDP-58 groups, respectively. RDP-58 was well tolerated. Most adverse events were mild or moderate and included nausea (10-50% for RDP-58 *vs.* 13% for placebo) and headache (7-39% for RDP-58 *vs.* 33% for placebo); these adverse events were dose-independent. The only serious adverse events reported were disease progression and leukopenia in 1 patient, which was unrelated to RDP-58 treatment. It was concluded that further studies involving increased dose and/or longer dosing should be initiated to determine the efficacy of RDP-58 as a treatment for Crohn's disease (37).

RDP-58 continues to undergo phase II development for Crohn's disease and ulcerative colitis. RDP-58 has also entered phase I trials for diarrhea and chemotherapy-induced mucositis, and development for GI complications of HIV infection has been proposed. Early preclinical studies have been initiated to determine the potential efficacy of RDP-58 as a treatment for psoriasis, multiple sclerosis and ophthalmic indications (37, 38).

Source

Genzyme Corp. (US) (developed by the former SangStat Medical Corporation, acquired last year by Genzyme).

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