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Alicaforsen Sodium

Prop INNM; USAN

Treatment of IBD
Antipsoriatic

ISIS-2302

2'-Deoxy-*P*-thioguanylyl-(3'→5')-2'-deoxy-*P*-thiocytidylyl-(3'→5')-2'-deoxy-*P*-thiocytidylyl-(3'→5')-2'-deoxy-*P*-thiocytidylyl-(3'→5')-2'-deoxy-*P*-thioadenylyl-(3'→5')-2'-deoxy-*P*-thioadenylyl-(3'→5')-2'-deoxy-*P*-thioguanylyl-(3'→5')-2'-deoxy-*P*-thiocytidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-deoxy-*P*-thioguanylyl-(3'→5')-2'-deoxy-*P*-thioguanylyl-(3'→5')-2'-deoxy-*P*-thiocytidylyl-(3'→5')-2'-deoxy-*P*-thioadenylyl-(3'→5')-2'-*P*-thiothymidylyl-(3'→5')-2'-deoxy-*P*-thiocytidylyl-(3'→5')-2'-deoxy-*P*-thiocytidylyl-(3'→5')-2'-deoxy-*P*-thioguanylyl-(3'→5')-2'-*P*-thiothymidylyl-(3'→5')-2'-deoxy-*P*-thiocytidylyl-(3'→5')-2'-deoxyadenosine nonadecasodium salt

CAS: 331257-52-4

CAS: 185229-68-9 (as free acid)

EN: 205912

Abstract

Alicaforsen sodium (ISIS-2302) is an antisense oligodeoxynucleotide that binds specifically to human ICAM-1 mRNA and induces its degradation. *In vitro* studies have shown that alicaforsen decreases the levels of ICAM-1 mRNA and protein by 20% and 30%, respectively. Toxicological studies have reported that alicaforsen activates the complement alternative pathway and induces changes in coagulation parameters in monkeys, but these effects take place at concentrations higher than those with pharmacological effects in mice. Clinical trials conducted to date have confirmed that alicaforsen is safe and effective in the treatment of inflammatory diseases such as psoriasis and Crohn's disease. However, further research is needed to evaluate the antiinflammatory effects of higher doses of alicaforsen and the possible use of a subcutaneous formulation in the treatment of Crohn's disease.

Synthesis

Alicaforsen can be obtained on an automated synthesizer such as Perseptive Biosystems Expedite 8901 or Pharmacia OligoPilot II DNA/RNA synthesizer, following a solid-phase strategy using DMTr (4,4'-dimethoxytrityl) as the 5'-*O*-nucleoside protecting group. The typical procedure used is based on standard deoxynucleoside phosphoramidite chemistry and replacement of the standard oxidation reagent by either 3*H*-1,2-benzodithiole-3-one 1,1-dioxide (Beaucage reagent) (1-4) or phenylacetyl disulfide (PADS) in acetonitrile/3-picoline (5) as sulfurizing reagents for the thiation of the phosphite linkage. The oligonucleotide is cleaved from resin in either concentrated NH_4OH at 55 °C or NH_3. Finally, alicaforsen sodium is purified by reverse-phase (1-5) or anion-exchange (6) chromatography.

Introduction

Psoriasis is an inherited chronic inflammatory cutaneous disorder characterized by papulosquamous lesions with epidermal cell hyperproliferation, infiltration of inflammatory cells and angiogenesis. Psoriatic lesions appear most frequently on the scalp, knees, elbows and torso, although the nails, palms, soles, genitals and face may also be affected. The lesions frequently appear in the same location on both sides of the body. Psoriasis affects approximately 2% of the population in the U.S. and Europe, and it is more prevalent in northern latitudes and less so in areas closer to the equator. Psoriasis affects men and women to an equal degree and can begin at any age, although the average age of diagnosis is 28 years. It is not an impairing disease, but it often has significant negative effects on self-esteem and social interaction of the patients. In patients with severe forms of the disease, where large portions of the body are affected, the skin's ability to regulate body temperature and prevent fluid loss may be seriously compromised and in extreme cases this may cause death.

Psoriasis is a T cell-dependent autoimmune disease that may be affected by genetic, immunologic and environmental factors. It has been suggested that the disease would be triggered in genetically predisposed individuals by an environmental stimulus, such as changes in climate, infections, stress, dry skin or some drugs. The psoriatic lesions seem to be caused by growth factors/cytokines released from activated epidermal T cells/keratinocytes. Aberrant keratinocyte ICAM-1 expression has been involved in the retention of T cells within the

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epidermis in many skin disorders. Therefore, the reduction or elimination of keratinocyte ICAM-1 *in vivo* could have significant therapeutic benefits with regard to T cell infiltration and activation in cutaneous immune disorders.

Crohn's disease is a very common form of inflammatory bowel disease (IBD) that involves chronic inflammation and ulceration in the intestines. Chronic and abnormal activation of the immune system leads to intestinal tissue destruction, which in the case of Crohn's disease extends deep into the intestinal wall and can involve the entire digestive tract, from the mouth to the anus. Approximately one in 1000 people suffer from IBD. This figure includes both Crohn's disease and ulcerative colitis; however, the incidence of Crohn's disease has increased 6-fold during the last 25 years. Antiinflammatory drugs constitute the primary therapy for IBD and they can help control disease by suppressing destructive immune processes and promoting healing of intestinal lesions.

Expression of a specific protein may be inhibited through the use of antisense oligonucleotides, short synthetic molecules usually 10-25 bases long that bind specifically to the mRNA encoding that protein. These oligonucleotides are often chemically modified to increase their stability towards cellular and serum nucleases, and therefore have one of the nonbridging oxygens in the phosphate backbone replaced with a sulfur; these are the so-called phosphorothioate oligonucleotides. Alicaforsen sodium (also known as ISIS-2302) is a 20-mer antisense phosphorothioate oligodeoxynucleotide that binds specifically to a sequence located in the 3' untranslated region of human ICAM-1 mRNA and induces its degradation, possibly through RNase H-mediated hydrolysis. These findings suggested that alicaforsen might be a promising new agent in the treatment of inflammatory diseases, such as psoriasis and Crohn's disease.

Pharmacological Actions

When human umbilical vein endothelial cells (HUVEC) were pretreated with 100 nM of alicaforsen for 4 h, the levels of ICAM-1 and mRNA induced by stimulation with TNF-α for 2 h were below 20 and 30%, respectively, of those measured in control cells (7). Pretreatment with 5 μM alicaforsen decreased ICAM-1 protein and mRNA expression in keratinocytes stimulated with gamma interferon, and the effects induced by alicaforsen increased when combined with 5 μg/ml lipofectin (8). Alicaforsen also inhibited VCAM-1 expression in HUVEC cells by 35% at 50 nM and by 65% at 100 nM. Cell adhesion experiments revealed that treating a HUVEC monolayer with alicaforsen decreased adherence of HL-60 cells (a human promyelocytic leukemia cell line) by 56% (7).

No *in vivo* preclinical studies have been conducted with alicaforsen in mice because its sequence is specific for the human ICAM-1 gene. Instead, a phosphorothioate oligonucleotide with an antisense sequence against the murine ICAM-1 gene (ISIS-3082) has been used. A murine inflammatory model of contact hypersensitivity reactions was used where 2,4-dinitrofluorobenzene (DNFB) was topically applied to the ear and the subsequent response was evaluated by measuring ear thickness and cellular infiltration. When no antiinflammatory agents were administered, ear swelling and cellular infiltration were maximal 24 h after the beginning of inflammation and they returned to normal values after 48-72 h and about 2 weeks, respectively. Intravenous administration of liposome-encapsulated ISIS-3082 at a dose of 50 mg/kg 15 min after DNFB challenge inhibited both ear swelling and cellular infiltration (as a control, i.v. administration of 50 mg/kg alicaforsen had no antiinflammatory effects). The antiinflammatory response to ISIS-3082 (5-50 mg/kg) was dose-dependent (9). Another study found that ISIS-3082 administered to mice treated with 5% dextran sodium sulfate (DSS) reduced the clinical signs of DSS-induced colitis in a dose-dependent manner, with maximal effects found with a dose of 1 mg/kg/day. Lower levels of ICAM-1 expression and leukocyte infiltration were found in the colon of mice treated with ISIS-3082. These results support the use of phosphorothioate oligonucleotides in the treatment of inflammatory bowel diseases in humans (10).

Pharmacokinetics and Metabolism

The pharmacokinetic parameters of alicaforsen are similar to those determined for other phosphorothioate oligonucleotides and are dose-dependent (Table I) (11, 12). After i.v. administration of alicaforsen (0.2-5.0 mg/kg), the elimination half-life in monkeys increased from 0.22 to 0.82 h and the AUC values increased from 0.37 ± 0.07 to 120.8 ± 17.8 μg·h/ml, whereas clearance decreased from 540.5 to 41.4 μg·h/ml. The elimination half-life values increased slightly when the drug was administered as a 2-h i.v. infusion instead of an i.v. bolus. Tissue distribution of the drug in monkeys also followed a dose-dependent pattern, and the highest concentrations were found in kidney, liver, spleen and lymph nodes (11). Clearance from tissues took place mainly by exonuclease degradation (13-15). The rate of clearance was slow (clearance half-live values for alicaforsen were 20-40 h in mice and 20-100 h in monkeys) and made daily dosing unnecessary for maintaining tissue exposure (15). All phosphorothioate oligonucleotides have a high affinity for plasma proteins and the unbound fraction of alicaforsen (1-2%) was much lower than those measured for other oligonucleotides. Similar protein affinity values have been measured in humans, monkeys and rodents (16). This association with plasma proteins prevents filtration through the kidneys and explains why very little intact alicaforsen is excreted through the urine (15).

A study compared the pharmacokinetics of two different doses of alicaforsen (1 or 5 mg/kg) administered to monkeys either i.v. (over 2 min) or s.c. The

Table I: Pharmacokinetic parameters after i.v. infusion of alicaforsen in cynomolgus monkeys [adapted from (11)].

Route	Dose (mg/kg)	$t_{1/2}$ (h)	AUC (μg·h/ml)	V_{ss} (ml/kg)	CL (ml·h/kg)
Bolus	0.2	0.22	0.37 ± 0.07	171.4	540.5
	1.0	0.29	16.2 ± 5.1	25.8	61.7
	2.0	0.47	21.4 ± 1.4	63.4	93.5
	4.0	0.68	74.6	51.5	53.5
	5.0	0.82	120.8 ± 17.8	49.0	41.4
2-h infusion	1.0	0.42	9.67 ± 0.19	71.4 ± 7.7	103.4 ± 2.1
	4.0	0.95	77.5 ± 2.9	69.2 ± 11.7	51.6 ± 1.9

$t_{1/2}$ = elimination half-life, AUC = area under the curve, V_{ss} = volume of distribution, CL = clearance.

Table II: Pharmacokinetics of alicaforsen in monkeys [adapted from (17)].

Dose (mg/kg)	Route	Dosing solution (mg/ml)	C_{max} (μg/ml)	t_{max} (h)	AUC (μg·h/ml)	CL (ml·h/kg)
1	i.v. bolus	10	36.8 ± 6.5	0.1 ± 0.05	16 ± 5	66 ± 20
1	s.c.	10	2.2 ± 1.0	0.7 ± 0.3	8 ± 3	62 ± 0.1
5	i.v. bolus	50	134.4 ± 21.9	0.1 ± 0.05	120 ± 18	42 ± 6
5	s.c.	50	9.2 ± 3.6	1.7 ± 0.8	66 ± 7	42 ± 0.1
5	s.c.	10	5.2 ± 1.8	1.7 ± 0.8	32 ± 14	42 ± 0

C_{max} = peak plasma concentration, t_{max} = time to peak plasma concentration, AUC = area under the curve, CL = clearance.

Table III: Pharmacokinetics of alicaforsen in human male volunteers after single infusion of 0.5 or 2.0 mg/kg over 2 h [adapted from (18)].

Dose (mg/kg)	V_{ss} (ml/kg)	AUC (μg/min/ml)	$t_{1/2}$ (min)	C_{max} (mg/ml)	C_{max}/dose (mg/ml)	CL (ml/min/kg)
0.5	155.4 ± 13.6	249.7 ± 43.8	54.4 ± 16.1	1.60 ± 0.16	3.21 ± 0.33	2.07 ± 0.48
2.0	97.5 ± 7.1	1824.6 ± 111.1	52.9 ± 6.0	10.3 ± 0.06	5.17 ± 0.34	1.28 ± 0.12

V_{ss} = volume of distribution, AUC = area under the curve, $t_{1/2}$ = plasma half-life, C_{max} = peak plasma concentration, CL = clearance.

pharmacokinetics of the different doses analyzed in this study are given in Table II. Subcutaneous administration of alicaforsen resulted in a C_{max} value that was less than 10% of that found after i.v. administration and much lower than the complement activation threshold (see below). After s.c. administration, a long absorption phase was followed by a slow decrease in plasma drug concentrations; plasma levels of parent drug decreased more slowly than after i.v. administration. The bioavailability of a s.c. dose of 5 mg/kg of alicaforsen was 55 ± 6% when administered at 50 mg/ml and 26 ± 11% at 10 mg/ml; therefore, higher concentrations administered in a small volume might be more suitable for achieving better bioavailability results. Overall, these results showed that s.c. injection was a valid route of administration for alicaforsen that resulted in the administration of an adequate amount of drug without complement activation in monkeys (17).

A phase I study analyzed the pharmacokinetics of i.v. alicaforsen (80 ml volume over 2 h) to 44 healthy male volunteers randomized to receive either placebo, single (0.06-2.0 mg/kg) or multiple (0.2-2.0 mg/kg) doses of alicaforsen. The pharmacokinetic parameters calculated for single doses of 0.5 and 2.0 mg/kg are shown in Table III. The distribution phase of alicaforsen was similar to that reported in different animal models. Shortened forms of the parent drug were detected in plasma very soon after i.v. administration and corresponded to 20% of total oligonucleotides at 30 min postinfusion. Nevertheless, the intact parent drug remained the most abundant oligonucleotide up to 250-350 min postinfusion. Very low levels of the parent drug and shortened forms were found in urine, and the estimated total excretion of the parent drug and metabolites over 6 h after beginning infusion amounted to less than 0.5% of the total dose. No accumulation in plasma was seen following multiple doses of alicaforsen (18). The plasma pharmacokinetics of alicaforsen in patients suffering from Crohn's disease were reported to be similar to those found in healthy volunteers (19).

The possible use of alicaforsen in the topical treatment of psoriasis prompted the study of the drug's pharmacokinetics as a topical cream. Topical alicaforsen quickly permeated rat, pig and human epidermis and dermis, where it accumulated. The skin half-life of intact alicaforsen was estimated to be 24 h in rats and 96 h in pigs, thus suggesting possible long-lasting effects. The efficacy of topical alicaforsen was confirmed by the drug's ability to dose-dependently inhibit ICAM-1 expression in human skin induced by intradermal injection of TNF-α (20).

Toxicology

Studies conducted using rodents revealed that phosphorothioate oligonucleotides share some common toxicologic properties suggestive of immune stimulation after systemic treatment. These appeared as dose-dependent clinical and anatomic pathological manifestations (*e.g.*, splenomegaly, lymphoid hyperplasia and hypergammaglobulinemia) found when mice were treated with alicaforsen doses ranging between 20 and 100 mg/kg. None of these manifestations were life threatening. Furthermore, these systemic effects seemed to be specific of rodents, as they were not found in monkeys receiving up to 50 mg/kg of alicaforsen for 4 weeks (15, 21, 22).

The administration of large systemic doses of phosphorothioate oligonucleotides to primates resulted in transient lethargy, periocular edema, susceptibility to bruising and hemodynamic alterations associated with activation of complement. A study revealed that administration of alicaforsen to monkeys (20 mg/kg i.v. over 10 min) resulted in a strong activation of the complement alternative pathway, with changes in hematologic and hemodynamic parameters possibly secondary to this activation. Increasing the duration of infusion or decreasing the dose of alicaforsen reduced the level of complement activation, as assessed using plasma concentrations of the complement split product Bb. Thus, peak Bb concentrations were 13, 3.25 and 1.5 μg/ml after infusion of 10 mg/kg of alicaforsen for 10, 30 and 60 min, respectively. No complement activation was found with some alicaforsen dose regimens, and Bb concentrations only changed once plasma concentrations of alicaforsen had exceeded a threshold of 50 μg/ml (23). This finding prompted the use of long i.v. infusion times in clinical trials in order to prevent drug levels from reaching the complement activation threshold and thus ensure safe administration.

Preclinical studies also showed that alicaforsen affects the values of coagulation parameters in monkeys. Intravenous infusion of 10 mg/kg of alicaforsen to monkeys over 2 min resulted in aPTT of about 160% over baseline values after 5 min, which then returned to baseline levels during the next 2 h. These effects correlated with alicaforsen plasma concentrations; however, aPTT remained essentially unaffected at plasma concentrations equal to or lower than 20 μg/ml of alicaforsen. The intrinsic coagulation pathway was affected more than the extrinsic pathway, as this same dose of alicaforsen increased prothrombin time to just 120% over baseline values (24). Alicaforsen binds to a site on factor IXa and inhibits the intrinsic tenase complex (factor IXa-factor VIIIa-phospholipid) needed for thrombin generation (25, 26). *In vitro* addition of alicaforsen to human or monkey plasma increased clotting times, and aPTT doubled at 100 μg/ml in monkey plasma and at 30-40 μg/ml in human plasma (27). This effect is independent of the nucleotide sequence but requires the phosphorothioate modification necessary for preventing degradation by nucleases, thus suggesting that it is a general property of all phosphorothioate oligonucleotides. Nevertheless, these coagulation changes were not clinically significant since the effects were transient, the increase in aPTT was less than 2-fold over baseline and only the intrinsic pathway was significantly affected.

Overall, alicaforsen has a good toxicity profile. The toxicity effects associated with blood coagulation and complement activation occur at concentrations higher than those inducing pharmacological effects in mice and are generally reversible after treatment discontinuation. Moreover, the similar toxicity profiles of alicaforsen and ISIS-3082 suggest that these effects are class-specific and unrelated to either ICAM-1 inhibition or the actual sequence of the oligonucleotide (15).

Clinical Studies

The efficacy of alicaforsen in the treatment of Crohn's disease was evaluated in a single-center, double-blind, placebo-controlled, randomized trial involving 20 patients with moderately active Crohn's disease who had not responded to treatment with corticosteroids and mesalamine drugs. The patients received i.v. infusions (over 2 h) of either placebo or 0.5, 1 or 2 mg/kg of alicaforsen in 100 ml of normal saline once every 2 days for 26 days. All patients administered alicafosen responded to treatment. Remission (defined as a Crohn's Disease Activity Index [CDAI] below 150) was seen in 7 (47%) alicaforsen-treated patients and 1 (20%) placebo-treated patient at the end of the treatment period. After 6 months of follow-up, 5 patients were still in remission and 1 patient had a CDAI of 156. The time to response and the duration of response were not affected by dose. Both placebo and alicaforsen induced improvements from baseline in the quality of life of the patients (as assessed by the Inflammatory Bowel Disease Questionnaire [IBDQ]), which were sustained with alicaforsen. The use of corticosteroids among alicaforsen-treated patients was significantly lower than among placebo-treated patients. Intestinal mucosal expression of ICAM-1 decreased in 9 of the 17 patients treated with alicaforsen, and changes in the expression of several adhesion molecules induced by alicaforsen indicated suppression of inflammation (19, 28). Retreatment of 7 of these patients with a second 26-day course of open-label alicaforsen between 6.5 and 12.5 months after the first course of therapy resulted in new remissions in 5 patients (29).

The results of this study and some that follow are summarized in Table IV.

A double-blind, placebo-controlled, randomized phase IIb trial enrolled 299 patients with steroid-dependent Crohn's disease who were randomly allocated to one of three treatment groups: placebo or alicaforsen (2 mg/kg/day i.v. infusion 3 times/week) for 2 or 4 weeks. Each patient received a course of treatment at the beginning of months 1 and 3. Overall, 20.2% of alicaforsen-treated patients and 18.8% of placebo-treated patients achieved complete clinical remission. However, the

Table IV: Clinical studies of alicaforsen (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Crohn's disease	Randomized double-blind	Alicaforsen, 0.5 mg iv over 2 h, 1/2d x 26 d Alicaforsen, 1 mg iv over 2 h, 1/2d x 26 d Alicaforsen, 2 mg iv over 2 h, 1/2d x 26 d Placebo	20	Alicaforsen appeared to change several adhesion molecules expression in patients with steroid-dependent Crohn's disease	28
Crohn's disease	Open	Alicaforsen, iv over 2 h, 1/2d x 26 d [second course of therapy]	7	Retreatment with alicaforsen was well tolerated and appeared to be effective in patients with Crohn's disease previously responding to it	29
Crohn's disease	Randomized, double-blind, crossover	Alicaforsen, 2 mg/kg/d iv infusion 3x/wk x 2-4 wk + Prednisone Placebo + Prednisone	229	Higher alicaforsen doses might be effective in Crohn's disease	30
Crohn's disease	Randomized, double-blind, multicenter	Alicaforsen, 0.5 mg/kg/d sc x 2 d (n=14) Alicaforsen, 0.5 mg/kg/d sc x 1 wk (n=17) Alicaforsen, 0.5 mg/kg/d sc x 2 wk (n=15) Alicaforsen, 0.5 mg/kg/d sc x 4 wk (n=14) Placebo (n=15)	75	Alicaforsen did not show clinical efficacy in achieving steroid-free remission in patients with active Crohn's disease and, although some positive trends were observed in other aspects of disease, the benefit of alicaforsen is questionable	31
Psoriasis	Randomized, double-blind, crossover	Alicaforsen 4%, top. od x 2 mo (n=15) Alicaforsen 4%, top. bid x 2 mo (n=16) Placebo (n=31)	31	Topical alicaforsen was well tolerated and appeared to improve induration and investigator global assessment in patients with active plaque-type psoriasis	32
Rheumatoid arthritis	Randomized, double-blind	Alicaforsen, 0.5 mg/kg iv 1/2d x 2 wk → 0.5 mg/kg iv 3x/wk x 2 (26 d) (n=10) Alicaforsen, 1.0 mg/kg iv 1/2d x 2 wk → 3x/wk x 2 wk (4 wk) (n=3) Alicaforsen, 2.0 mg/kg iv 1/2d x 2 wk → 3x/wk x 2 wk (4 wk) (n=19) Placebo (normal saline) iv 1/2d x 2 wk → 3x/wk x 2 wk (4 wk) (n=11)	43	Infusion of alicaforsen was well tolerated in patients with active rheumatoid arthritis. Efficacy was not evident on the final day of treatment (26 d), probably because of the low serum drug exposure in the study patients	33
Renal transplant	Randomized, double-blind, crossover	Alicaforsen, 0.05 mg/kg iv over 2 h x 8 doses Alicaforsen, 0.05 mg/kg iv over 4 h x 8 doses Alicaforsen, 0.05 mg/kg iv over 6 h x 8 doses Alicaforsen, 0.5 mg/kg iv over 2 h x 8 doses Alicaforsen, 0.5 mg/kg iv over 4 h x 8 doses Alicaforsen, 0.5 mg/kg iv over 6 h x 8 doses Alicaforsen, 1 mg/kg iv over 2 h x 8 doses Alicaforsen, 1 mg/kg iv over 4 h x 8 doses Alicaforsen, 1 mg/kg iv over 6 h x 8 doses Alicaforsen, 2 mg/kg iv over 2 h x 8 doses Alicaforsen, 1 mg/kg iv over 4 h x 8 doses Alicaforsen, 2 mg/kg iv over 6 h x 8 doses Placebo	16	Alicaforsen was well tolerated and effective but a slower rate of infusion is recommended to avoid the dose-related increase in aPTT	34

subgroup of patients with the highest drug exposure (assessed by AUC values and corresponding to heavier patients and females) showed a remission rate of 55.6%; these patients also had better clinical response and quality of life scores than patients with low AUC values (30). A phase III clinical trial is currently under way to assess the efficacy of higher doses of alicaforsen, modeled on the AUC values found for responding patients in the this trial.

A double-blind, randomized, placebo-controlled phase II trial assessed the efficacy of 4 different dose regimens of alicaforsen administered s.c. to 75 patients with steroid-dependent Crohn's disease. At week 14, complete clinical remission (defined as CDAI below 150 and complete discontinuation of steroid treatment) was found in 3.3 and 0% of alicaforsen- and placebo-treated patients, respectively. At week 26, these rates increased to 13.3 and 6.7%, respectively. Compared to placebo, a higher percentage of patients treated with alicaforsen showed low dose steroid-dependent remission, clinical remission or clinical response, but the differences were not statistically significant and were not dose-related. Further studies are needed to assess the validity of s.c. administration of alicaforsen in the treatment of Crohn's disease (31).

A double-blinded, paired-plaque, randomized, placebo-controlled pilot study determined the efficacy of a 4% topical formulation of alicaforsen on 31 patients suffering from active plaque-type psoriasis vulgaris affecting up to 20% of total body surface. Two index plaques were chosen from each patient; one of them was treated with placebo and the other with the alicaforsen formulation for 2 months. According to the investigator global response score, the percentages of patients who responded better to alicaforsen than to placebo were 40 and 24% after 4 and 8 weeks of treatment, respectively. Induration scores also improved with alicaforsen (32). These results suggest that phosphorothioate oligonucleotides may play a role in the treatment of skin diseases, either alone or in combination with other medications, and further trials on this subject are currently under way.

Preliminary efficacy data for alicaforsen in the treatment of rheumatoid arthritis has recently been published (33). In this double-blind, placebo-controlled, dose escalation study, patients with rheumatoid arthritis were randomized to receive either placebo or 0.5, 1 or 2 mg/kg of alicaforsen. The drug's efficacy was estimated using the Paulus composite score, a well-accepted measure of improvement in rheumatoid arthritis symptoms. On day 26 of the study, the early placebo response was high (36%) but not significantly different from that found among alicaforsen-treated subjects. The average intent-to-treat Paulus 20% responses for study months 2-6 were 21.1% for alicaforsen and 12.6% for placebo. Only 19% of alicaforsen-treated subjects and no placebo-treated subjects showed Paulus 50% responses during the study. This study lacked the statistical power necessary for reaching firm conclusions on the efficacy of alicaforsen. However, the authors believe that this may have been caused by suboptimal dosing (as the subjects were receiving less than half of the optimal drug exposure reported in Crohn's disease studies) and hence suggest that future studies on rheumatoid arthritis should use higher alicaforsen doses (33).

The good safety profile of alicaforsen in preclinical studies has been confirmed by several clinical studies. A phase I clinical trial conducted in 44 healthy male volunteers assessed the safety of single and multiple i.v. doses of alicaforsen. A dose-related increase in aPTT was found that was only clinically significant with the highest doses. In all treatment groups, aPTT increased with drug infusion, reached maximum at 1-2 h after beginning the infusion and returned to baseline at 2-4 h after beginning the infusion. The highest aPTT increases were found in the group of subjects receiving single or multiple doses of 2.0 mg/kg. Both prothrombin and thrombin times also increased after alicaforsen administration but the differences were small and clinically insignificant. Slight evidence of complement activation (measured by median C3a concentrations) was found after administration of some of the higher doses of alicaforsen, but in all cases the increases were not clinically relevant and parameters returned to baseline at 4 h after beginning drug infusion. No serious adverse events were reported (18). These results were compared with those found by another double-blind, placebo-controlled phase I study, in which 8 i.v. infusions of alicaforsen (0.05-2 mg/kg over 2, 4 and 6 h) are administered to 44 quiescent cyclosporine-prednisone-treated renal transplant patients. Compared to healthy volunteers, these patients showed similar changes in PTT and coagulation parameters, but the C3a levels remained unaltered after drug administration. Again, no adverse events were reported (34). Clinical trials conducted to assess the efficacy of alicaforsen in psoriasis, Crohn's disease and rheumatoid arthritis have also reported good safety results, with transient dose-related increases in aPTT (19, 29, 32, 33).

Source

Isis Pharmaceuticals, Inc. (US).

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