A Randomized, Placebo Controlled Trial of an Antisense Oligodeoxynucleotide to Intercellular Adhesion Molecule-1 in the Treatment of Severe Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To determine the safety of an antisense oligodeoxynucleotide to intercellular adhesion molecule-1 (ICAM-1) (ISIS 2302), administered in an intensive 4 week regimen with dose escalation; and to provide preliminary evidence for efficacy in rheumatoid arthritis (RA).

Methods. Patients with active RA were enrolled in a 6 month, double blind, placebo controlled, dual center, dose escalation (0.5, 1, and 2 mg/kg) study. Subjects received a total of 13 intravenous ISIS 2302 infusions, given on alternate days for 2 weeks and then 3 times a week for another 2 weeks. Doses of corticosteroids (≤ 10 mg/day) and disease modifying antirheumatic drugs (stable ≥ 3 months) remained constant throughout the study. The primary efficacy endpoint was the Day 26 Paulus index, with secondary evaluations at Months 2–6.

Results. A total of 43 patients were enrolled with 11, 10, 3, and 19 patients receiving placebo or 0.5, 1, or 2 mg/kg of ISIS 2302, respectively. There were no differences between groups after randomization and the mean baseline swollen joint count was 22.5. Pharmacokinetic studies revealed a $T_{1/2}$ of 63 min and first-order kinetics with slight dose dependency, suggesting a saturable clearance process, although no accumulation was noted with repeat dosing. The Paulus 20% responses at Day 26 were 20%, 0%, and 5% for patients treated with ISIS 2302 (0.5, 1, 2 mg/kg, respectively) and 36% with placebo. For Months 2–6, the average intent-to-treat Paulus 20% responses were 21.2% for ISIS 2302 and 12.6% for placebo. Only ISIS 2302 treated subjects (19%) achieved Paulus 50% responses. ISIS 2302 was well tolerated. An expected and transient mean activated partial thromboplastin time increase of roughly 7 s was observed at the highest dose (2 mg/kg), as were small and clinically insignificant increases in serum C3a levels. T/B cell immunophenotyping, recall antigen skin testing, and serum immunoglobulin levels revealed no significant immunosuppressive effects.

Conclusion. This study shows that 13 ISIS 2302 infusions over 4 weeks are well tolerated in patients with active RA. Although significant efficacy was not evident at the primary endpoint (1 month), the study lacked sufficient power to draw any formal conclusions. We tested a 4-fold drug concentration range, which led to a lower area under the curve range than was therapeutic in a subsequent Crohn's disease trial. Any further evaluation of this well tolerated ICAM-1 antisense agent should therefore be conducted at higher dosing. (J Rheumatol 2002;29:447–53)

Key Indexing Terms:
RHEUMATOID ARTHRITIS CLINICAL TRIAL ANTISENSE DEOXYNUCLEOTIDE

Intercellular adhesion molecule-1 (ICAM-1; CD54) is an inducible transmembrane glycoprotein and a member of the immunoglobulin superfamily that is constitutively expressed at low levels on vascular endothelial cells and a subset of leukocytes[1,2]. It is upregulated on many cell types in response to proinflammatory stimuli, including interleukin 1 and tumor necrosis factor-α (TNF-α)[3]. $ß_2$-integrins, leukocyte function associated antigen 1 (LFA-1), and Mac-1, all expressed on leukocytes, are the primary ligands for ICAM-1[4,5]. A primary role of ICAM-1 is to facilitate firm adhesion of leukocytes to the vascular endothelium at sites of inflammation, followed by transmigration into the extravascular space[6-13]. It also provides one of a number of costimulatory signals involved in the activation of T cells and other leukocytes[9,11-15]. ICAM-1 therefore constitutes a potential molecular target for direct therapeutic intervention in rheumatoid arthritis (RA).

ISIS 2302 is a 20 base phosphorothioate oligodeoxynu-

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Dr. Maksymowych is a Scholar with the Alberta Heritage Foundation for Medical Research.

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Submitted May 7, 2001; revision accepted September 11, 2001

cleotide (Figure 1) designed to specifically hybridize to a sequence in the 3' untranslated region of human ICAM-1 message RNA (mRNA)[16]. RNase-H, a ubiquitous family of nucleases, uniquely recognizes oligodeoxynucleotide-RNA heterodimers, resulting in RNA cleavage (Figure 2) with a highly specific reduction in ICAM-1 mRNA and consequent ICAM-1 expression[17]. Phosphorothioate modification of the oligodeoxynucleotide, substituting a sulfur molecule for a nonbridging oxygen molecule in each phosphodiester linkage (Figure 1), significantly increases the general exonuclease resistance over unmodified DNA and prolongs the drug half-life[18].

ISIS 2302 selectively inhibits cytokine induced ICAM-1 expression in a variety of human cells *in vitro* and *in vivo*[19]. ISIS 2302 pharmacokinetics in human volunteers showed a dose dependent plasma distribution half-life ($T_{1/2}$) of 30–80 min, with minimal urinary excretion[20]. Two-hour infusions (dose range 0.06–2 mg/kg) repeated every other day for 4 doses were well tolerated. In nonhuman primates, ISIS 2302 is rapidly distributed to the extravascular space, with subsequent uptake by tissues; tissue half-life ranged from 1 to 5 days in different tissues, depending on rates of metabolism via exonucleases[21,22]. A murine analog, ISIS 3082, showed dose dependent therapeutic effects in collagen induced arthritis[23].

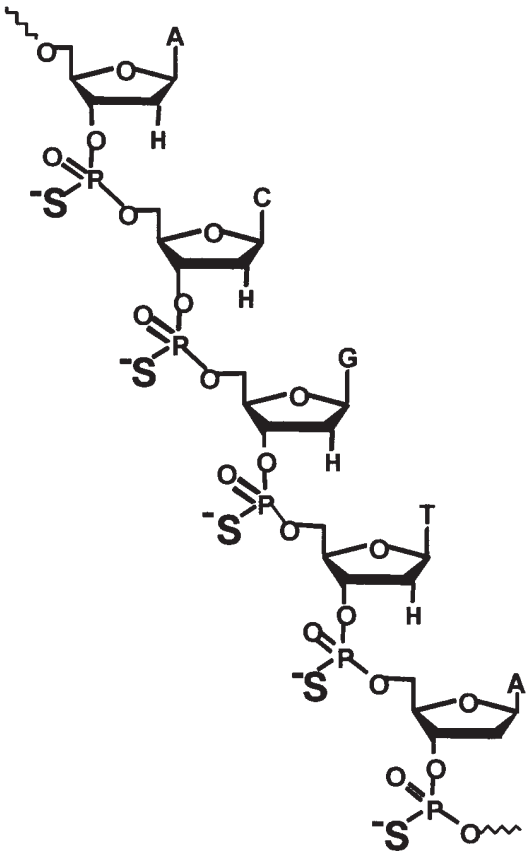

Figure 1. Chemical structure of a phosphorothioate oligodeoxynucleotide. A sulfur molecule substitutes for a nonbridging oxygen molecule in each phosphodiester linkage.

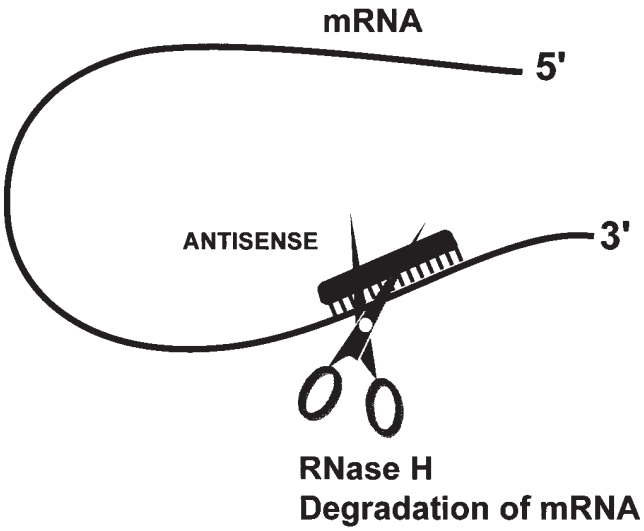

Figure 2. Specific binding of ISIS 2302 antisense oligodeoxynucleotide to ICAM-1 mRNA results in RNA cleavage by RNAse-H.

In summary, the *in vitro*, animal, and phase I studies support a preliminary safety and efficacy evaluation of a unique ICAM-1 antisense agent, ISIS 2302, in patients with severe RA. Pharmacokinetic data in nonhuman primates showed no plasma accumulation when 2 mg/kg was administered intravenously on a daily basis for up to 28 days[21,22]. This dose is also within the therapeutic range in animal models[23]. Transient prolongation of the activated partial thromboplastin time (aPTT) and alternative complement pathway activation leading to the production of C3a and C5a due to the binding of oligonucleotide to plasma proteins have been observed in monkeys, and constitute nonspecific class effects of all phosphorothioate oligonucleotides[24,25]. It was estimated that 2 mg/kg would result in peak plasma levels about 20–30% of the threshold for complement activation. Together with the pharmacokinetic data documenting a tissue half-life of 1–5 days[21], these studies formed the basis for the development of a dose escalation regime evaluating 0.5–2.0 mg/kg on alternate days for initial evaluation in human RA.

MATERIALS AND METHODS

Overall study design. This was a 6 month, randomized, double blinded, placebo controlled phase I/II study of ISIS 2302 in patients with active RA. After a 2 week run-in period, patients were randomized in a 3:1 ratio to receive either study drug or saline placebo for 4 weeks. The dose escalation study originally called for 4 patients each in the 0.5 mg/kg and 1.0 mg/kg groups, and then 12 patients in the 2.0 mg/kg group, if the original doses were well tolerated. The protocol was subsequently amended to include additional recruitment of patients into the 0.5 mg/kg and 2.0 mg/kg groups in view of preliminary data from the prespecified interim analysis that suggested efficacy at these doses. Subjects were evaluated on a monthly basis. The study protocol and subsequent amendments were approved by the Research Ethics Board of the University of Alberta and the Institutional Review Board of the University of Alabama School of Medicine. An

interim analysis for safety and efficacy was planned when 50% of the subjects completed the study.

Patients. The trial enrolled patients aged 18 to 78 years old. Patients met the American College of Rheumatology (ACR) diagnostic criteria for RA[26] and had symptoms of RA for > 6 months. Active disease was defined by the presence of > 10 swollen joints and at least 2 of the following 3 criteria: > 12 tender joints, morning stiffness > 1 h, or erythrocyte sedimentation rate (ESR) > 25 for men and > 35 for women. Required background therapy consisted of nonsteroidal antiinflammatory agents (NSAID), unless NSAID intolerant, at stable doses for one month prior to study entry. Low dose corticosteroids ≤ 10 mg were allowed provided the dose had been stable for one month prior to study entry. Patients could receive a disease modifying antirheumatic drug (DMARD), provided the dosage had been stable for 3 months prior to study entry. Doses remained constant for the duration of the study. Exclusion criteria were pregnancy or lactation, intraarticular steroids within 2 months prior to study entry, white blood cell count < 3.5×10^9/l, platelet count < 100×10^9/l, hemoglobin < 9.5 g/dl for women or < 10.5 g/dl for men, abnormal liver function tests, abnormal renal function, other serious disease, investigational drug therapy in the previous month, patients with radiologic or endoscopic evidence of active peptic ulcer disease, or a reliable history of gastrointestinal bleeding within the past year. Precautions regarding the exclusion of patients with active peptic ulcer disease were considered necessary in view of the transient prolongation of aPTT observed with all phosphorothioate oligonucleotides.

Randomization. Treatments were assigned in blocks of 4 with a 3:1 ratio (active:placebo) per cohort. A computer generated the randomization list, using the RANUNI function and PROC rank with SAS version 6.12 for OS/2. Randomization codes were provided to the investigational drug pharmacist to allow proper drug mixture. The investigators were provided with sealed envelopes, each marked with a patient number, that contained the randomization code assigned to that patient number in the event of an emergency. As the investigator could potentially become unmasked upon reviewing postinfusion aPTT results, the investigational sites were blinded to the results of coagulation assays drawn after the screening visit. The central laboratory reviewed the aPTT assays and contacted the sponsor if any aPTT result was > 2 times control.

ISIS 2302 administration. ISIS 2302 was formulated at 10 mg/ml in a sterile aqueous preservative-free solution with a pH of 7.28. Placebo consisted of 0.9% sodium chloride solution (normal saline). Drug or placebo was administered IV over 2 h. Patients received ISIS 2302 or placebo every other day for 2 weeks, followed by 3 times a week for the following 2 weeks.

Efficacy assessment. The primary efficacy measure was the Paulus composite score (this composite was the RA trial standard at the time of the Investigational New Drug submission)[27]. Secondary clinical efficacy measures examined included the following: change from baseline in the number of swollen joints among 66 diarthrodial joints, number of tender/painful joints on motion among 68 diarthrodial joints, patient's assessment of disease activity (1–5 scale), investigator's assessment of disease activity (1–5 scale), patient's assessment of pain (visual analog scale, VAS), duration of morning stiffness, grip strength (JAMAR hand dynamometer), functional capacity (American Rheumatism Association-Steinbrocker criteria), ESR (University of Alberta used Wintrobe, University of Alabama used Westergren), and C-reactive protein (CRP). Since the active treatment period was only 1 month and since the primary objective of the study was the assessment of safety, more detailed assessment of physical function was not performed. Clinical assessments were done at screening, baseline, and at each review visit, or at any time the patient was discontinued from the study. If the patient received at least one IV infusion of study drug, the patient remained in the study through Month 6, with efficacy evaluations at Weeks 1, 2, and 4, and then monthly following the discontinuation of study drug therapy.

Withdrawals. A patient was to be withdrawn from therapy if a serious side effect occurred that was related to study drug, early inadequate therapeutic effect occurred requiring a dosage increase or addition of concomitant antiarthritic medication during the 4 weeks of study drug therapy, or therapeutic failure was documented. Flare criteria for withdrawal were specified but not utilized by any subject.

Pharmacokinetics. Samples were obtained at 0, 30, 60, 120, 130, 145, 180, and 240 min after the start of infusion on Days 1, 7, and 26. In addition, an end of infusion concentration was obtained on Days 3, 13, and 19. ISIS 2302 and its chain-shortened metabolites were measured in plasma using a capillary gel electrophoresis method[28]. Plasma pharmacokinetics were analyzed using a noncompartmental method using WinNonlin 1.5 software. C_{max} was the maximal plasma concentration for each patient, and the area under the plasma concentration-time curve (AUC) was calculated using the linear trapezoidal rule with extrapolation to time-infinity. ISIS 2302 plasma half-life ($T_{1/2}$) was calculated from $T_{1/2lz} = 0.693/l_z$, where l_z is the slope of the terminal plasma concentration-time curve.

Safety measurements. Safety assessments were completed at every visit, including an examination of vital signs during and 2 h after the IV infusion. Laboratory data included rheumatoid factor, complete blood count, liver and renal function tests, urinalysis, coagulation studies (aPTT, prothrombin time, PT), fibrinogen, D-dimer, complement activation products (C3a and C5a), peripheral blood lymphocyte subsets (CD3, CD4, CD8, CD19), antigen recall skin tests (at least 3 of tetanus, diphtheria, streptococcus, tuberculin, candida, trichophyton, and proteus) and serum immunoglobulins. A centralized laboratory (Covance Central Laboratory Services, Indianapolis, IN, USA) was used for evaluation of the majority of the laboratory measurements. Complement activation product in plasma was analyzed in a research facility (T. Hugli, PhD, Scripps Research Institute, La Jolla, CA, USA), with normal ranges of C3a < 1125 ng/ml and C5a < 12.2 ng/ml. ISIS 2302 plasma concentrations were performed by Covance Hazelton (Madison, WI, USA). Measurement of soluble circulating ICAM-1 levels was by ELISA (R. Rothlein, PhD, Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT, USA[29]).

Statistical analysis. All patients randomized to receive treatment who received at least one IV infusion of ISIS 2302 were included in the efficacy analyses. If a patient withdrew from treatment at any time, the last available values were carried forward. The primary endpoint was the last day of study drug infusion (i.e., Day 26). The study was not powered to detect significant differences between the treatment groups and no formal conclusions regarding efficacy were to be drawn. For assessing changes from baseline, the treatments were compared by analysis of variance using the SAS (v. 6.12) Windows NT statistical package. Response rates according to the Paulus 20% and 50% criteria were compared by chi-square test. P values are reported without adjustments for multiple comparisons. The primary safety analysis was performed on adverse events using a COSTART dictionary.

RESULTS

A total of 43 patients were enrolled in this study and 40 completed the study; all 43 patients were entered into the efficacy analysis. They were randomized to the 4 treatment groups as follows: placebo (n = 11), ISIS 2302 0.5 mg/kg (n = 10), ISIS 2302 1.0 mg/kg (n = 3), and ISIS 2302 2.0 mg/kg (n = 19). The demographic characteristics in the different treatment groups were similar (Table 1). Most patients were seropositive (86%), functional class II, had erosive disease, and were previous DMARD failures. Overall, most patients (84%) were receiving DMARD; the majority continued to receive methotrexate (MTX) alone (49%) or in a DMARD combination (12%). The baseline swollen and tender joint counts were 22.5 and 35.6, respectively.

Of the 43 patients enrolled, 3 did not receive all 13 doses.

Table 1. Demographic details.

	Placebo	ISIS 2302 Dosage Group 0.5 mg/kg	1 mg/kg	2 mg/kg	All Rx
No. of subjects	11	10	3	19	32
Age, yrs	60.2	55.8	67.8	56.3	57.3
% Female	54.5	70	100	57.9	65.6
RA duration, yrs	14.7	10.7	10.0	15.4	13.6
Rheumatoid factor, %	82	100	100	79	88
Swollen joints	19.7	22.5	27.3	23.4	23.5
Tender joints	35.6	34.3	49.0	34.3	35.7
Corticosteroid,%	64	60	33	42	47
DMARD (range)	4.3 (2–10)	4 (1–8)	1.3 (0–2)	2.8 (0–7)	2.9 (0–8)

One patient (2 mg/kg) had received 11 of 13 doses prior to discontinuing treatment for increased severity of a preexisting problem with dizziness and syncope. The other 2 missed a single dose. During treatment, there were 2 protocol violations: one patient (placebo, 13 doses) increased her prednisone dose and another patient (2 mg/kg, 12 doses) increased his DMARD and prednisone dosages. One placebo subject received a single 2 mg/kg ISIS 2302 dose on Day 13. During followup, one subject started MTX at Month 4.5, one varied his MTX dose for several weeks, and 3 subjects received intraarticular corticosteroid injections.

Table 2 documents the number of patients whose disease responded according to the Paulus 20% composite index. A significant, early placebo response was observed (36%) for the last day (Day 26) of this intensive IV administration period, which fell to 9% at Month 2. There was no significant difference by Day 26 between patients receiving placebo and study agent. From Months 2 to 6, the average Paulus 20% response rates were 28%, 27%, and 16.8% in the 0.5, 1.0, 2.0 mg/kg groups, respectively, 21.2% in the combined ISIS 2302 group, and 12.6% in the placebo group (p = NS). Six ISIS 2302 (19%) and no placebo subjects achieved a Paulus 50% response (one in 0.5 mg/kg, one in 1.0 mg/kg, and 4 in 2.0 mg/kg), all occurring between Days 60 and 180 (Table 2). These responders did not include those patients who had protocol-excluded therapeutic interventions during the followup period.

Pharmacokinetic analysis revealed that C_{max} occurred at the end of the infusion period and ranged from 1.8 to 10.5 µg/ml for the study dosages. Mean plasma AUC rose from 3.8 (± 1.1) to 23.5 (± 11.6) µg*h/ml as the ISIS 2302 dosage increased from 0.5 to 2 mg/kg. The increase in C_{max} and AUC was greater than the increase in dose. Taken together with a slight increase in plasma $T_{1/2}$, as dose increased from 40 + 10 min at 0.5 mg/kg to 63 + 21 min at 2 mg/kg, these data indicate saturation of a plasma clearance pathway. The most likely explanation is saturable distribution into peripheral tissues. There were no changes in $T_{1/2}$, AUC, or C_{max} with repeat dosing.

Adverse events that were possibly related to treatment occurred in 54% of all patients and none were severe (Table 3). Only one patient (2 mg/kg) experienced possibly related adverse events (nausea, dizziness, excessive sweating)

Table 2. Clinical response by Paulus criteria. Data in parentheses are percentages.

	Placebo	ISIS 2302 dosage group 0.5 mg/kg	1 mg/kg	2 mg/kg	All RX
No. of subjects	11	10	3	19	32
Paulus 20%					
Month 1 (Day 26)	4 (36)	2 (20)	0	1 (5)	3 (9)
Month 2	1 (9)	1 (10)	0	2 (11)	3 (9)
Month 3	3 (27)	2 (20)	1 (33)	5 (26)	8 (25)
Month 4	1 (9)	3 (30)	1 (33)	4 (21)	8 (25)
Month 5	1 (9)	4 (40)	1 (33)	1 (5)	6 (19)
Month 6	1 (9)	4 (40)	1 (33)	4 (21)	9 (28)
Paulus 50% (overall)					6 (19)
Month 2				1 (5)	
Month 3				3* (16)	
Month 5		1 (10)			
Month 6			1 (33)	1* (5)	

* One subject met Paulus 50% criteria at Months 3 and 6.

Table 3. Adverse events reported in ≥ 10% of subjects. Data in parentheses are percentages.

Adverse Event Category	ISIS 2302 Dosage Group				
	Placebo	0.5 mg/kg	1 mg/kg	2 mg/kg	All Rx
No. of subjects	11	10	3	19	32
Central nervous system					
Headaches	3 (27)	3		5	8 (25)
Dizziness	4 (36)	1		4*	5 (16)
Gastrointestinal					
Abdominal pain	4 (36)	1	1	3	5 (16)
Nausea	4 (36)	2		7	9 (28)
Diarrhea	2 (18)		1	7	8 (25)

* One subject withdrew after 11 infusions for increased baseline dizziness.

leading to study drug discontinuation. The most common adverse events in ISIS 2302 subjects were diarrhea, headache, and dizziness, some recurrent with subsequent infusions. There were no differences compared to subjects taking placebo. The reported serious adverse events, all considered unrelated to study drug, included surgery for progressive RA (one each in placebo and 0.5 mg/kg ISIS 2302), basal cell carcinoma (0.5 mg/kg ISIS 2302), elective coronary angiography (2 mg/kg ISIS 2302), and accidental fractures (placebo). There were no changes in vital signs or other physical findings with ISIS 2302 infusions.

Serum ICAM-1 levels during the trial did not vary significantly for ISIS 2302 subjects compared to placebo. C3a and C5a levels were elevated erratically, on both pre- and postinfusion testing, suggesting ambient samples with handling problems. However, evaluation of the differences between mean pre- and postinfusion values for each treatment group revealed small, dose responsive increases in C3a but not C5a that did not change with the number of infusions. There were no clinically significant events or changes in vital signs associated with these small C3a increases. The postinfusion aPTT values increased roughly 7 s in the 2 mg/kg patients (Table 4), which was significant compared to background placebo variability of roughly ± 0.5 s ($p < 0.001$). The maximal individual aPTT increase after a 2 mg/kg infusion was 35 s. There was no correlation between the postinfusion aPTT increase and the number of prior infusions received. There were no clinically significant events associated with aPTT increases, and no change in fibrinogen, prothrombin time, or D-dimer levels. There were no significant changes in routine chemistries, T cell (CD3, CD4, CD8) or B cell (CD19) populations, recall antigen skin tests, or serum IgG, IgA or IgM levels.

DISCUSSION

This report describes the first experience with an ICAM-1 antisense oligodeoxynucleotide, ISIS 2302, on clinical, laboratory, and immunologic variables in patients with RA. This phase I/II study was not statistically powered to allow firm conclusions regarding efficacy. A significant placebo response was reported (36%) for the last day (Day 26) of this intensive IV administration period, which fell to 9% at Month 2. This is in keeping with observations from trials investigating intensive regimens of IV study agent administration[30]. No significant differences in efficacy variables were evident at Day 26. However, only ISIS 2302 treated subjects (19%) achieved Paulus 50% responses, occurring between Days 60 and 180. Subjects may have been undertreated even in the 2 mg/kg group, with their mean drug exposure (AUC) of 23.5 (± 11.6) µg*h/ml. Data from a recent Crohn's disease trial suggest that an exposure of ≥ 65 µg*h/ml may be needed for optimal response[31]. A 5-fold variation in ISIS 2302 drug exposure was observed, although all patients received the same 2 mg/kg dosage, with drug exposure being markedly increased in heavier patients and women. Although there was no difference in remission rates between the active and placebo groups, a retrospective analysis revealed a significant correlation

Table 4. Mean change from baseline in postinfusion aPTT (± SD) for all infusions.

	ISIS 2302 Dosage Group				
	Placebo	0.5 mg/kg	1 mg/kg	2 mg/kg	All Rx
No. of subjects	11	9	3	19	31
Group mean aPTT posttransfusion changes, seconds	0.55 (± 1.7)	3.99 (± 1.3)	5.87 (± 4.1)	7.93 (± 3.6)*	4.77 (± 4.0)
Range in individual mean aPTT changes (average all infusions)	–1.9–3.5	1.7–6.3	2.9–10.6	2.32–14.5	1.7–14.5

*$p < 0.001$ versus placebo.

between individual patient responses and their drug AUC, with the highest rate of response being observed in the small number of subjects who achieved an AUC ≥ 65 µg*h/ml. Our subjects received less than half of the optimal drug exposure reported in the Crohn's trial, and may also have shown less antiarthritic effect due to suboptimal dosing.

ISIS 2302 appears to be a very safe modality, consistent with reports that have now examined over 500 individuals who received this agent[20,31,32]. An increased frequency of headaches, nausea, dizziness, and diarrhea were noted, but were generally regarded as mild and of questionable relation to study drug, as similar frequencies were noted in placebo treated patients. The primary drug related laboratory finding was a mean aPTT increase of 7 s at the end of infusion for the 2 mg/kg group, with a maximum prolongation of 35 s for a single infusion. The aPTT changes returned to baseline within 6 h after infusion, and no cumulative aPTT effect was observed with repeated dosing. The prolonged aPTT is secondary to inhibition of intrinsic tenase complex (factors IXa and VIIIa, phospholipid, and calcium) activity[33]. In addition, clinically silent, small increases in activated complement C3a split products were noted at the 2 mg/kg dose, previously shown to be due to alternative pathway activation by an interaction with inhibitory protein factor H[24]. No changes in C5a, Bb, C4d, or factor H were recorded in the healthy volunteer study, despite small increases in C3a with repeated dosing at 1 and 2 mg/kg[20]. Our highest study dose of 2 mg/kg achieved C_{max} values in the range of 10–15 µg/ml, which is far below the reported threshold level of 40–50 µg/ml for complement activation in monkeys[25]. Both C3a and aPTT changes are dose related class effects of all phosphorothioate oligodeoxynucleotides, observed in monkeys[25] and healthy volunteers[20] receiving ISIS 2302. Dose related increases in aPTT have also been reported in subjects with Crohn's disease treated with ISIS 2302[31,32].

ISIS 2302 was very well tolerated during an intensive IV regimen. This study represents the first report of a systemically administered ICAM-1 antisense compound, ISIS 2302, in RA. Efficacy was not evident on the final day of treatment (Day 26) and the study showed a high placebo response rate (36%) on that day. The lack of efficacy could be secondary to the relatively low serum drug exposure (AUC) achieved in these patients. Any further development of this agent for RA should include higher dosages and seek to simplify the drug administration regimen.

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