Effects of Recombinant Soluble Type I Interleukin-1 Receptor on Human Inflammatory Responses to Endotoxin

By Hugh L. Preas II, Debra Reda, Margaret Tropea, R. William Vandiver, Steven M. Banks, Jan M. Agosti, and Anthony F. Suffredini

INTERLEUKIN-1 (IL-1) has a central role in the regulation of inflammatory responses to infection. Patients with sepsis and animals with experimental infection have elevated blood levels of IL-1β and when administered to animals or humans, IL-1 causes a syndrome resembling sepsis that includes fever, hypotension, leukocytosis, and increased vascular permeability. Blocking cell-associated IL-1 receptors with IL-1 receptor antagonist (IL-1ra) can neutralize IL-1 effects and result in improvement of hypotension and organ failure in septic animals. The administration of endotoxin to normal humans reproduces many of the cardiovascular and inflammatory responses of sepsis. We used this model to evaluate whether the administration of sIL-1R1 would alter the clinical and inflammatory manifestations of acute endotoxemia. Our results demonstrate an interaction between sIL-1R1 and circulating IL-1ra in vivo that may limit the antiinflammatory effects of sIL-1R1, as well as IL-1ra and result in enhancement of some inflammatory responses.

MATERIALS AND METHODS

Subjects and study plan. Thirteen men and five women, 19 to 35 years of age (mean, 26 years) were evaluated. With the exception of one woman taking oral contraceptives, none were taking any medications, and all had normal physical examinations, electrocardiograms, chest radiographs, and blood and urine analyses. The study was approved by and performed in accordance with the ethical standards of our institutional review board on human experimentation. Written consent was obtained from all the subjects. Study participants were admitted to the medical intensive care unit after fasting overnight and given maintenance intravenous (IV) fluids.

The subjects were randomized to receive a 30-minute infusion of either placebo (sIL-1R1, vehicle, n = 6), 1 mg/m² (n = 6), or 10 mg/m² (n = 6) of sIL-1R1 (Immunex Corp, Seattle, WA). A prior study in normal volunteers had shown that a dose of 1 mg/m² resulted in a mean maximum concentration of 0.48 µg/mL of sIL-1R1 with a mean T1/2 of 17.3 hours. A dose of 10 mg/m² was associated with a mean maximum concentration of 5.02 µg/mL of sIL-1R1 and a mean T1/2 of 15.3 hours. These doses were not associated with any significant clinical or laboratory abnormalities including induction of serum antibodies directed against sIL-1R1. Higher doses (>20 mg/m²) administered in this previous pharmacokinetic study were associated with allergic reactions.

The recombinant human IL-1R1 was produced in a mammalian expression system (NS1 cells). The truncated soluble form of the IL-1R1 was engineered by isolating the cDNA, which encoded the N-terminal 312 amino acids of full-length IL-1R1 protein. A CAV-neo- S-rhu IL-1R expression cassette, introduced into a murine myeloma cell line (NS1), produced sIL-1R1 as a glycoprotein with a molecular weight of 59 ± 2 kDa. The receptor is a monomer in solution and binds one mole of IL-1 per mole of receptor and forms a stable complex between a single truncated receptor molecule and a single IL-1 molecule. The soluble IL-1R1 binds IL-1 with high-affinity, equal to the binding affinity of the intact, membrane form of IL-1R1.

The sIL-1R1 was supplied as a sterile lyophilized preparation of...
0.5 mg or 2.5 mg recombinant human protein per vial with 40 mg mannitol, USP; 10 mg sucrose, NF; and 1.2 mg tromethamine (Tris), USP. The placebo contained only the inactive excipients. The sIL-1R, or placebo was reconstituted with 1 mL of sterile Water for Injection (USP), diluted in 100 mL of 0.9% saline and infused for 30 minutes. Following the infusion, purified lipopolysaccharide prepared from *Escherichia coli* O113 (U.S. Standard Reference Endotoxin, Lot EC-5, Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, MD) was administered IV (4 ng/kg of body weight, n = 18) over 1 minute and flushed with 10 mL of 0.9% saline.

Oral temperature (Diatek, San Diego, CA), respiratory rate, heart rate, and blood pressure were measured at 15-minute intervals. Blood pressure was continuously monitored with radial artery catheters (Arrow International, Redding, PA). The number and severity of symptoms (chills, headache, arthralgia, myalgia, nausea) were assessed at the end of each study day based on a scale of absent—0, mild—1, moderate—2, or severe—3.

Systemic hemodynamic responses were evaluated further in the placebo subjects and those given high-dose sIL-1R. Central pressures and cardiac output were assessed with pulmonary artery catheters (VIP, Baxter Healthcare, Edwards Critical Care Division, Irvine, CA) and ventilatory function was evaluated with radionuclide (technetium-99 m) heart scans as previously described. Systemic hemodynamics were measured at baseline (0 hour), 3 hours, 5 hours, and 8 hours after endotoxin administration. To assess ventilatory function at different preloads, fluid loading was performed using 0.9% saline (10 U/mL blood; Abbott, Chicago, IL) and serum samples were collected on subsequent study days. Plasma samples were anticoagulated with nonpyrogenic heparin, Lot EC-5, Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, MD) and blood was drawn at 5 hours after the endotoxin infusion to raise the pulmonary artery occlusion pressure by at least 3 mmHg.

To estimate dissociable IL-1Rα complexed with sIL-1Rα, plasma samples were assayed by immunosassay (R & D Systems) after a 30-minute incubation at 37°C with a neutralizing anti-human IL-1Rα monoclonal antibody (M1; Immunex) and 50 μg/mL final antibody concentration.

C-reactive protein was measured by radial immunodiffusion assay (The Binding Site, Birmingham, UK) with a detection limit of 0.033 mg/L. Serum amyloid A was measured by immunoassay (Biosource, Camarillo, CA) with a detection limit of 9.4 mg/mL. Lactoferrin was assayed by ELISA as previously described. The detection limit of the ELISA was 1 ng/mL plasma.

Endotoxin-stimulated whole blood was used to assess the effects of sIL-1Rα on cytokine production in vitro. Blood from four additional normal subjects was collected in heparinized syringes (nonpyrogenic heparin 10 U/mL blood, Abbott, North Chicago, IL) and plated in 12-well culture plates (Costar, Cambridge, MA). Blood samples were stimulated with lipopolysaccharide 1 μg/mL (St. minnesota; Sigma, St. Louis, MO) following the addition of sIL-1Rα (final concentration 0.5, 5, 15 μg/mL). These concentrations of sIL-1Rα were based on levels achieved in earlier clinical trials following the administration of 1, 10, or 30 mg/m², respectively. The plates were incubated on a rocking platform at 37°C with 5% CO₂. Samples for cytokines were assayed after 0, 1, 4, 8, 16, and 24 hours of incubation using immunoassays (all R & D Systems).

**RESULTS**

**Systemic and clinical responses.** All 18 subjects given endotoxin developed fever, constitutional symptoms, and re-

---

From www.bloodjournal.org by guest on October 27, 2017. For personal use only.
Temperature occurred at 6 hours and the magnitude and pattern of the fever did not differ among the groups. Chills were less severe in subjects given sIL-1R compared with low-dose sIL-1RI or placebo significantly lower in subjects given high-dose sIL-1RI compared with placebo subjects. Increases in neutrophil band forms and decreases in platelet counts were not altered by high-dose sIL-1RI; no significant differences were found between the placebo and high-dose sIL-1RI groups.

Data from subjects given low and high doses of sIL-1R were statistically similar and the results are pooled for presentation (mean ± sem). Abbreviation: NS, not significant.

Baseline values for all subjects were statistically similar.

† Change over time in both placebo and sIL-1R subjects.

Cytokine and acute phase protein responses. In subjects given endotoxin and placebo, low levels of IL-1β were present at baseline and a small increase occurred at 3 hours in the placebo subjects (10.6 ± 2.8 pg/mL). No increase occurred in subjects given sIL-1R, and this was significantly different than placebo (P = .0001, Fig 1A). Cell-associated IL-1β rose significantly at 3 hours (P = .0001) and was greater in high-dose sIL-1R subjects than placebo and low-dose sIL-1R subjects (P = .047, Fig 1B). IL-1ra was significantly lower in subjects given high-dose sIL-1R compared with low-dose sIL-1R or placebo (P = .0001) and these changes were maximum at 3 hours (Fig 1C). At 3 hours, complexes of IL-1Rα-IL-1ra in subjects given high-dose sIL-1R were 43-fold greater (P = .0001) and in low-dose 10-fold greater than placebo (P = .001) (Fig 2). Incubation of blood samples from all subjects given endotoxin (with and without sIL-1R) with anti-sIL-1R antibody (M1, 5 μg/mL) resulted in a significant increase in measurable IL-1ra at 3 hours in all three groups (amount of increase in IL-1ra above 3-hour IL-1ra levels; placebo 110.2 ± 11.3, low-dose 122.0 ± 17.3, high-dose 138.0 ± 12.7 ng/mL, dose ordered P < .001). Increased amounts of the neutralizing M1 antibody (50 μg/mL) did not increase the amount of dissociable IL-1ra (data not shown).

Elevated levels of TNF-α cytotoxicity were present at 1.5 to 2 hours in all three groups (P = .0001) and were statistically similar among the groups (maximum, placebo 202 ± 94, low-dose 217 ± 133, high-dose 364 ± 196 pg/mL, P = NS). TNF-α immunoactivity rose with maximum values at 1.5 to 2 hours in all three groups (P = .001). Subjects given high-dose sIL-1R had higher levels than subjects given low-dose sIL-1R or placebo (P = .02, Fig 3A). IL-8 levels were maximum at 2 to 3 hours in all three groups and were greater in subjects given high-dose sIL-1R than in subjects given low-dose sIL-1R and placebo (P = .0001, Fig 3B). IL-6 levels rose (P = .0001) with maximum values at 3 hours and were statistically similar among the three groups (placebo 2,477 ± 1,653, low-dose 1,514 ± 516, high-dose 3,124 ± 1,550 pg/mL, P = NS). G-CSF levels rose (P = .0001) with maximum values at 3 to 6 hours and were statistically similar among the three groups (placebo 2,761 ± 1,824, low-dose 2,045 ± 577, high-dose 2,057 ± 1,488 pg/mL, P = NS). IL-1ra levels correlated positively with both TNF-α immunoactivity (r values similar for all three groups, P > .5, average r = 0.81, P < .001) and IL-8 (r values similar for all three groups, P > .5, average r = 0.61, P < .02).

In vitro, the effects of adding sIL-1R to normal donor serum treated with EDTA and spiked with 20 pg/mL of
Additional of a 1,000-fold excess of sIL-1R1 (20 ng/mL) re-
resulted in 93% ± 7% recovery of IL-1β, while 10⁶-fold excess of
sIL-1R1 (20 μg/mL, similar to levels achieved in blood after
4.8 mg/kg IV) decreased the recovery of IL-1β to
67% ± 6%. Small concentrations of sIL-1R1 also interfered
with the measurement of IL-1ra in human serum (n = 3):
IL-1ra spiked alone into human sera resulted in 77% ± 5%
IL-1ra recovery (2.3 ± 0.15 ng/mL), while only 35% ± 4%
(1.06 ± 0.12 ng/mL) of IL-1ra was recovered after incuba-
tion with sIL-1R1. The blocking effect of sIL-1R1 on IL-1ra
measurements was reversed by incubation of IL-1ra and sIL-
1R1 with a neutralizing anti–sIL-1R1 antibody (M1) (74% ±
6% recovery, 2.23 ± 0.18 ng/mL).

To assess effects of increasing doses of sIL-1R1 (0, 0.5,
5, 15 μg/mL) on cytokine production in vitro, whole blood
was stimulated with endotoxin in the presence of placebo or
sIL-1R1 (n = 4). Maximum levels occurred at 16 hours. A
dose-ordered decrease in IL-1ra (301 ± 258, 51 ± 4.8, 0.03
± 0.019, and 0.022 ± 0.016 ng/mL; P = 0.05) and IL-6 (201
± 29, 184 ± 36, 171 ± 24, and 153 ± 15 ng/mL; P = 0.01)
occurred following doses of 0, 0.5, 5, and 15 μg/mL of sIL-
1R1, respectively. No significant differences were observed
in levels of IL-8, IL-1β, or TNF among the three in vitro
doses of sIL-1R1 and placebo (data not shown).

**DISCUSSION**

The administration of sIL-1R1 before IV endotoxin had
only limited antiinflammatory effects manifested by de-
creased severity of chills without decreasing other constitu-
tional symptoms. Other parameters including fever, hemody-
namic responses, alterations in leucocyte and platelet
number, as well as secondary markers of inflammation (eg,
lactoferrin, IL-6, and G-CSF levels) were not altered by sIL-
1R1 administration. However, sIL-1R1 did result in decreased
levels of IL-1β and IL-1ra, and the latter was associated
with a dose-related increase in sIL-1R1-IL-1ra complexes. In
subjects given high-dose sIL-1R1, these interactions were
associated with increased levels of cell-associated IL-1β,
plasma TNF-α, and IL-8 immunoactivity, and increased C-
reactive protein levels compared with placebo. Thus, sIL-
1R1 resulted in the binding of IL-1β and IL-1ra and enhance-
ment of some inflammatory responses during endotoxemia.

Soluble cytokine receptors may antagonize cell signaling
by competing with membrane-associated receptors for their
respective ligands. Examples include soluble IL-4 receptor and
TNF-α receptor.11,30 Alternatively, other soluble cyto-
kine receptors, after associating with their ligands such as
IL-6 receptor or ciliary neurotrophic factor receptor, can
initiate cell signaling by associating with a dimeric form of the
gp130 signal transducing unit.11-13 Soluble IL-1 receptors
have differing antagonist or agonist roles, depending on their
affinities for IL-1 and IL-1ra. IL-1α, IL-1β, and IL-1ra all
bind IL-1R, with high-affinity. Because of a slow dissocia-
tion rate, IL-1ra binds more avidly than IL-1α or IL-1β to
soluble IL-1R1.34-35 The binding of IL-1ra by sIL-1R1 thus
represents an indirect mechanism of agonist activity elicited
by a soluble cytokine receptor; IL-1ra, the endogenous inhib-
or of IL-1, is neutralized, and this may result in unopposed
IL-1 effects and a net agonist response.36 In contrast, IL-
1R2, a “decoy receptor” that does not initiate cell signaling
after binding IL-1, is24,29 binds IL-1α (and IL-1α) with low-
avidity and a fast dissociation rate, but binds IL-1β with high-avidity.34,35 Thus, interactions of IL-1R1 with IL-1ra
are unlikely to interfere with the ability of either to inhibit
effects of IL-1β.24,29 The importance of the interactions of
both type I and II IL-1R with IL-1 has been shown in vitro.
IL-1ra inhibition of IL-1–induced collagenase and prosa-
glandin E₂ (PGE₂) production by dermal fibroblasts or syto-
vial cells was attenuated by type I IL-1R, but not type II IL-
1R.36

**Table 2. Hemodynamics Following Endotoxin and sIL-1R, Administration (10 mg/m²)**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>sIL-1R1</th>
<th>P Value</th>
<th>Placebo</th>
<th>sIL-1R1</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl (L/min·m²)</td>
<td>3.0 ± 0.3</td>
<td>3.4 ± 0.2</td>
<td>0.0001</td>
<td>NS</td>
<td>6.1 ± 0.2</td>
<td>6.4 ± 0.2</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>59 ± 3</td>
<td>71 ± 4</td>
<td>0.0001</td>
<td>NS</td>
<td>98 ± 4</td>
<td>102 ± 3</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>92 ± 5</td>
<td>87 ± 5</td>
<td>0.007</td>
<td>NS</td>
<td>85 ± 5</td>
<td>76 ± 6</td>
</tr>
<tr>
<td>SVRI (dyn·sec/cm⁵·m²)</td>
<td>2.178 ± 11</td>
<td>1.847 ± 167</td>
<td>0.0001</td>
<td>NS</td>
<td>984 ± 52</td>
<td>963 ± 82</td>
</tr>
<tr>
<td>EF (%)</td>
<td>59 ± 3</td>
<td>57 ± 3</td>
<td>0.0001</td>
<td>NS</td>
<td>61 ± 4</td>
<td>59 ± 3</td>
</tr>
<tr>
<td>VO₂ (mL/min·m²)</td>
<td>141 ± 16</td>
<td>135 ± 9</td>
<td>0.0001</td>
<td>NS</td>
<td>225 ± 28</td>
<td>177 ± 18</td>
</tr>
<tr>
<td>DO₂ (mL/min·m²)</td>
<td>552 ± 67</td>
<td>575 ± 62</td>
<td>0.0001</td>
<td>NS</td>
<td>942 ± 65</td>
<td>940 ± 41</td>
</tr>
<tr>
<td>O₂ ER (%)</td>
<td>17 ± 1</td>
<td>16 ± 1</td>
<td>0.0001</td>
<td>NS</td>
<td>15 ± 1</td>
<td>13 ± 1</td>
</tr>
</tbody>
</table>

**Abbreviations and formulae:** Cl, cardiac output/body surface area; HR, heart rate; MAP, mean arterial pressure; SVRI, systemic vascular resistance index; EF, left ventricular ejection fraction; arterial or mixed venous oxygen content (CaO₂, CvO₂) = [Hgb x 1.34 x % sat] + [PO₂ x 0.0031]; VO₂, oxygen consumption = Cl x (CaO₂ - CvO₂); DO₂, oxygen delivery = Cl x CaO₂; O₂ ER, oxygen extraction ratio = (CaO₂ - CvO₂)/CaO₂.

* Maximum or minimum for each variable occurred 5 hours after endotoxin, except for MAP (3 hours). The amounts of fluid administered for volume loading between 3 hours and 5 hours were similar between groups (placebo 3.4 ± 0.2 vs sIL-1R1 3.3 ± 0.5 L).

† Change over time in both placebo and sIL-1R1 subjects.

From www.bloodjournal.org by guest on October 27, 2017. For personal use only.
Fig 1. Serum IL-1β (A), cell-associated IL-1β (B), and plasma IL-1ra (C) after endotoxin administration in subjects randomized to receive placebo, low-dose, or high-dose sIL-1R. Data presented as mean ± SEM and analyzed by three way ANOVA. A small, but significant, increase in IL-1β occurred in placebo subjects compared with both low- and high-dose IL-1β (P = .0001). Cell-associated IL-1β was greater in high-dose sIL-1R, subjects compared with placebo and low-dose sIL-1R, subjects (P = .047). IL-1ra was lower after high-dose sIL-1R compared with low-dose sIL-1R, or placebo subjects (P = .0001).

Fig 2. IL-1R-IL-1ra complexes 3 hours after endotoxin administration in subjects randomized to receive placebo, low-dose, or high-dose sIL-1R. Data presented as mean ± SEM and analyzed by three way ANOVA. Levels of complexes after high-dose sIL-1R were 43-fold greater (P = .0001) and after low-dose sIL-1R were 10-fold greater than in placebo subjects (P = .001).

Fig 3. TNF-α immunoactivity (A) and IL-8 (B) after endotoxin administration in subjects randomized to receive placebo, low-dose, or high-dose sIL-1R. Data presented as mean ± SEM and analyzed by three way ANOVA. Subjects given high-dose sIL-1R had higher levels of TNF-α than placebo subjects given low-dose sIL-1R, or placebo (P = .02). IL-8 levels were greater in subjects given high-dose sIL-1R, than in subjects given low-dose sIL-1R, and placebo (P = .0001).
duction of other cytokines. Concentrations of IL-1ra similar to those generated in vivo with IL-2 infusions are sufficient to downmodulate production of IL-1β and TNF-α by IL-2–stimulated peripheral blood mononuclear cells. In the current study, the greatest reduction in IL-1α levels occurred 1 to 2 hours after the augmented release of immunooactive TNF-α and IL-8. It is likely that changes in circulating IL-1ra are detected later than those in the immediate cell environment. Antigenic TNF levels were increased, but the observed increase in TNF cytotoxicity was not statistically significant. This may be due to greater variability observed in the TNF bioassay compared with the immunooassay. It is unknown whether the increased levels of antigenic TNF were due to increased TNF receptor shedding. IL-1ra infusions during experimental human endotoxemia did not decrease TNF type I receptor levels. The effect of decreased IL-1α levels, as observed in this study, on TNF receptor shedding is unknown. Correlations of maximum IL-1ra with TNF-α and IL-8 levels were positive and did not differ among the placebo and sIL-1Rα subjects. Therefore, in vivo, it appears that IL-1ra depletion alone did not account for the augmented levels of TNF-α and IL-8. Presumably other mediators contributed to the increased TNF-α and IL-8 levels.

Other studies that have attempted to limit IL-1 effects during experimental human endotoxemia have had only limited success. A continuous infusion of IL-1ra in subjects challenged with 2 ng/kg of endotoxin resulted in a decrease in symptom severity but not decreases in fever or heart rate. Other studies with IL-1ra infusion have described a reduction in neutrophilia without changes in symptoms or vital signs after 3 ng/kg of endotoxin. The use of sIL-1Rα in our study was associated solely with a decreased severity of chills. Although IL-1 may contribute to the development of symptoms, the results above describing the effects of a pure IL-1 antagonist (IL-1ra) demonstrate the redundancy of inflammatory pathways during initial responses to endotoxin. IL-1 produced in extravascular sites may limit the effects of circulating inhibitors. Alternatively, IL-1 may have a relatively minor role in the acute manifestations of endotoxemia. Some investigators have found IL-1β only at low levels in extracted plasma, while others have not found increases in circulating levels in human subjects following endotoxin administration. In the current study, high levels of sIL-1Rα in vitro blunted the detection of IL-1β in spiked samples. Thus, the absence of a rise in IL-1β after sIL-1Rα infusion may be due to binding of IL-1β or in part to the effects of sIL-1Rα excess on the immunomodulatory process.

Soluble cytokine receptors, including type I and II TNF receptors, as well as IL-1Rα, are detectable in the circulation during the acute inflammatory response to endotoxin as well as sepsis. An IL-1 binding protein with similarities to IL-1Rα has been described in normal serum and may be a fragment of IL-1Rα. We found low levels of complexed sIL-1Rα-IL-1ra in the placebo subjects at 3 hours postendotoxin, and IL-1ra could be dissociated from the complex by an anti-IL-1R antibodies. No increase in IL-1ra was found in preendotoxin baseline samples treated with the antibody. These results suggest that, during the peak inflammatory response to endotoxin, low levels of IL-1Rα are released into the circulation.

Soluble IL-1Rα, has been effective in experimental models of inflammation including arthritis, transplantation, encephalomyelitis, and human allergic response, although its interactions with IL-1ra in these specific models has not been described. The beneficial effects observed in these models could be related to the dose of sIL-1Rα. Consistent with this possibility is the observation that both low- and high-dose sIL-1Rα decreased IL-1β levels, but, unlike high-dose sIL-1Rα, low-dose sIL-1Rα did not decrease IL-1ra levels. Increasing the dose of sIL-1Rα during acute endotoxemia would likely lead to larger reductions in IL-1ra and result in greater unopposed IL-1 effects. This might exacerbate inflammatory responses in a manner similar to the use of anti–IL-1ra antibodies in models of acute and chronic inflammation. Our data show that during the acute phase response to endotoxin, when there is a 100-fold greater release of IL-1ra than of IL-1β into the circulation, sIL-1Rα will have essentially no antiinflammatory effect due to low levels of circulating IL-1β and neutralization of IL-1ra inhibitory function. These results emphasize that the dosing of soluble cytokine receptors can result in unexpected agonist interactions during the acute phase response to endotoxin, and these may limit some of their therapeutic applications.

REFERENCES


35. Arend WP, Malayak M, Smith MF Jr, Whisenand TD, Slack JL, Sims JE, Giri JL, Dower SK: Binding of IL-1alpha, IL-1beta, and IL-1 receptor antagonist soluble IL-1 receptors and levels of soluble IL-1 receptors in synovial fluids. J Immunol 153:4766, 1994


40. Granowitz EV, Clark BD, Vannier E, Callahan MV, Dinarello CA: Effect of interleukin-1 (IL-1) blockade on cytokine synthesis: I. IL-1 receptor antagonist inhibits IL-1-inducible cytokine synthesis and blocks the binding of IL-1 to its type II receptor on human monocytes. Blood 99:3356, 1992


42. Tigg H, Shapiro L, Vannier E, Poutsiaakos DD, Trehe E, Atkins MB, Dinarello CA, Mier JW: Induction of circulating antagonists to IL-1 and TNF by IL-2 administration and their effects on IL-2-induced cytokine production In vitro. J Immunol 152:3189, 1994


53. Svenson M, Hansen MB, Heegaard P, Abell K, Bendtzen K: Specific binding of interleukin 1 (IL-1)/β and IL-1 receptor antagonist (IL-1ra) to human serum. High affinity binding of IL-1ra to soluble IL-1 receptor type I. Cytokine 5:427, 1993


Effects of recombinant soluble type I interleukin-1 receptor on human inflammatory responses to endotoxin

HL 2nd Preas, D Reda, M Tropea, RW Vandivier, SM Banks, JM Agosti and AF Suffredini