Depletion of α/β T Cells by a Monoclonal Antibody against the α/β T Cell Receptor Suppresses Established Adjuvant Arthritis, but not Established Collagen-induced Arthritis in Rats

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Summary

The effects of treatment with a monoclonal antibody (R73 mAb) against T cell receptor α/β (TCR-α/β) on both established adjuvant arthritis (EAA) and established collagen-induced arthritis (ECIA) in rats have been investigated. Rats were treated with R73 mAb when arthritis reached a peak. Treatment with the anti-TCR-α/β mAb markedly suppressed EAA, whereas ECIA was not affected by the mAb treatment. Histologically, R73 mAb–treated rats with EAA showed mild hyperplasia of synovial tissues, sparse infiltration of inflammatory cells, and minimal erosion of cartilage, whereas arthritic rats treated with PBS and an irrelevant control mAb against Giardia had marked hyperplasia of synovium with pannus, massive inflammatory cell infiltrate, and severe destruction of cartilage and subchondral bone. R73 mAb–treated rats with ECIA exhibited pronounced formation of pannus containing many inflammatory cells and marked cartilage and subchondral damage similar to those in arthritic rats that received the control treatments. Treatment with R73 mAb depleted markedly α/β$^+$ T cells in both peripheral blood and synovial tissues of rats with EAA and ECIA. R73 mAb treatment was associated with marked reduction in arthritogen-specific delayed-type hypersensitivity responses in both EAA and ECIA. The titers of antibodies against type II collagen produced in rats with ECIA were not affected by the mAb. Thus, α/β$^+$ T cells appear to have a central role in EAA, but not in chronic ECIA.

R heumatoid arthritis (RA)[1] is a chronic destructive inflammatory joint disease for which key inducing agents have not been identified. Although a number of investigations have shown that T cells are a prominent cell in rheumatoid synovium (1–3), humoral factors including rheumatoid factor and anti–type II collagen antibodies are also prominent and there is no direct evidence that implicates T cells as a necessary participant in the established or postinduction phase of the disease.

Both adjuvant arthritis (AA) and collagen-induced arthritis (CIA) in rats are experimental models of polyarthritis that resemble RA in certain clinical and histological aspects (4, 5). AA and CIA can be induced by immunization with *Mycobacterium tuberculosis* (MT) (4) and native type II collagen (CII) (5), respectively, and are believed to be mediated by T cells. For instance, lymph node and spleen cells from rats primed with MT and CII passively transfer AA (6) and CIA (7), respectively, to naive recipient rats, although the recipients develop a less persistent, milder arthritis than is

observed in rats immunized actively with the antigens. T cell lines and clones specific for MT (8) and CII (9) can also cause mild transient arthritis. These studies indicate that T cells are necessary for the induction of the both forms of arthritis, but do not examine directly the role of T cells in the established diseases. To determine whether T cells have a role in established AA (EAA) and established CIA (ECIA), we have assessed the effects on these diseases of a mAb (R73 mAb) against a constant determinant of TCR-α/β that is expressed on 97% of rat peripheral blood T cells (10). We report here that the depletion of α/β$^+$ T cell by treatment with R73 mAb suppressed EAA, while ECIA was not affected by the mAb, indicating that T cells play a crucial role in EAA, but not in ECIA.

Materials and Methods

Animals. Inbred female Dark Agouti rats weighing 90–100 g were purchased from Gilles Plains Animals Resource Center (Gilles Plains, South Australia). They were housed five per cage and fed standard rodent chow (Milling Industries, Dulwich, South Australia) and water ad libitum.

Induction of AA and CIA. AA was induced by an intradermal

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[1] *Abbreviations used in this paper:* AA, adjuvant arthritis; CIA, collagen-induced arthritis; CII, type II collagen; DTH, delayed-type hypersensitivity; E, established; MT, *Mycobacterium tuberculosis*; RA, rheumatoid arthritis.

injection into the tail base of 0.1 ml of CFA containing 10 mg/ml MT (R73Ra; Difco Laboratories, Detroit, MI). To induce CIA, 8 mg of CII extracted from native calf articular cartilage (Elastin Products, MO) was dissolved in 1 ml of 0.01 M acetic acid and emulsified with an equal volume of IFA. 0.1 ml of the emulsion was injected into the tail base. AA was established by day 14 and CIA by day 20 after injection of the appropriate arthritogen. To evaluate the severity of arthritis, the lesions of the four paws were each graded from 0 to 4 according to the increasing extent of erythema and edema of the periarticular tissue as described by Wood et al. (11). The maximum possible score is 16.

Treatment with R73 mAb. The cell line of a mouse mAb (R73 mAb) against the constant determinant of TCR-α/β kindly provided by Dr. T. Hünig (Würzburg, FRG). R73 mAb was purified from ascitic fluid according to the method of Ey et al. (12). The preparation and characterization of R73 mAb have been described previously (10). 100 μg of R73 mAb dissolved in 1 ml of PBS was injected intraperitoneally on days 14, 15, 16, 17, 18, 20, and 22 in rats with EAA, and on days 20, 21, 22, 23, 24, 26, and 28 in rats with ECIA. To assess whether the induction of both AA and CIA is blocked by treatment with R73 mAb, the antibody was given every 3 d from the time of immunization with MT and CII up to days 21 (AA) and 27 (CIA), respectively. As treatment controls, 1 ml of PBS only and 1 ml of PBS containing 100 μg of a mouse mAb (1B5 mAb) against Giardia (Department of Microbiology and Immunology, University of Adelaide, Adelaide, Australia), which is the same isotype (IgG1) as R73 mAb but has irrelevant specificity, were given to comparable groups of rats at the above times.

Histology. Rats with EAA were killed on day 14 (before R73 mAb treatment) and day 24 (after treatment), and rats with ECIA were killed on day 20 (before treatment) and day 30 (after treatment). Hind paws were amputated, fixed in 4% formalin, and decalcified in a solution of 3.1% HCl, 5% formic acid, and 7% aluminium chloride. The tissues were embedded in paraffin, sectioned at 4 μm, and stained with hematoxylin and eosin.

Detection of Peripheral Blood α/β^+ T Cells. A small volume of blood was withdrawn immediately before the next injection of R73 mAb from the tail vein for preparation of smears on days 14, 18, and 24 after immunization with MT and on days 20, 24, and 30 after immunization with CII. To detect α/β^+ and CD5$^+$ T cells, smears were incubated with R73 and OX19 mAbs (anti-CD5; Department of Microbiology and Immunology, University of Adelaide, Adelaide, Australia), respectively, and bound antibodies were revealed using F(ab')$_2$ fragments of sheep anti-mouse IgG antibody (Sigma Chemical Co., St. Louis, MO) and complexes of alkaline phosphatase and a murine mAb against alkaline phosphatase (APAAP; Boehringer Mannheim, North Ryde, New South Wales, Australia) according to the method of Cordell et al. (13). Fast red was used as a capture agent to detect cells labeled by APAAP and hematoxylin was the counterstain. The percentage of leukocytes binding R73 and OX19 mAb was determined.

Immunohistology. To determine whether α/β^+ T cells in synovial tissues of rats with EAA and ECIA are depleted by treatment with R73 mAb, 100 μg of the mAb was given intraperitoneally into five rats on days 14–17, and on days 20–23 after immunization with MT and CII, respectively. PBS and 1B5 mAb were given to treatment control rats. The animals were killed 7 h after the last injection of R73 mAb or control treatment, and ankle joints were amputated. The ankle joints were immersed in an EDTA solution for decalcification according to the method of Jonsson et al. (14) and frozen for the preparation of 7 μm cryosections. α/β^+

and CD5$^+$ (OX19 mAb$^+$) T cells in the joint synovial tissues were detected by the APAAP method as described above.

Induction of Delayed-Type Hypersensitivity (DTH). 20 μg of MT suspended in 50 μl of PBS and 20 μg of CII dissolved in 50 μl of 0.001 M acetic acid was injected subcutaneously into the right ear on day 18 in rats immunized with MT and on day 24 in rats immunized with CII, respectively. As vehicle controls, 50 μl of PBS or 50 μl of 0.001 M acetic acid alone was injected into the left ear. The thickness of the right and left ears were measured using dial gauge calipers calibrated with 0.01-mm graduations (Mitutoyo, Japan) immediately before and 48 h after the challenge injection of MT or CII. There was minimal ear swelling after 48 h in response to MT and CII in nonimmunized rats. The increase in left ear thickness was subtracted from the increase in right ear thickness, to determine swelling attributable to the specific response to antigen.

Measurement of Anti-CII Antibody. Blood was collected on days 20, 25, and 30 after immunization with CII as described above. Sera were heat inactivated at 56°C for 30 min, and stored at -20°C until assayed. Anti-CII antibody was measured using an ELISA (15). In brief, 96-well flat-bottomed microtiter plates were incubated with 100 μl/well of CII (20 μg/ml) at 37°C for 1 h and washed three times with PBS containing 0.05% Tween 20. The wells were then blocked by incubation with 200 μl of PBS containing 1% BSA at 37°C for 1 h. After washing, the plates were incubated with 100 μl/well of twofold dilutions of pooled rat sera at 37°C for 30 min. The plates were washed, and 100 μl/well of a 1:250 dilution of sheep anti–rat IgG labeled with β-galactosidase (Amersham, North Ryde, NSW, Australia) was added and incubated at 37°C for 30 min. After washing, 100 μl of 3 mM o-nitrophenyl-β-D-galactopyranoside (Amersham) was added per well and the plates were incubated in the dark at room temperature for 30 min. The absorbance was then measured at 410 nm in a Titertec ELISA reader (Flow Laboratories, North Ryde, NSW, Australia). Antibody titers were expressed as $-\log_2$ dilution at which an absorbance of two times control (omitting rat serum) was obtained.

Results

Effect of R73 mAb on EAA and ECIA. EAA developed by day 14 after immunization with MT (Fig. 1 A). Rats given repeated injections of PBS and 1B5 mAb from day 14 exhibited persistent active disease. In contrast, one injection of R73 mAb on day 14 had significantly suppressed existing arthritis 24 h later. Marked progressive suppression of arthritis followed the further administration of R73 mAb on days 15, 16, 17, 18, 20, and 22.

Typically, ECIA became evident on day 20 after immunization with CII (Fig. 1 B). Treated rats with R73 mAb on days 20, 21, 22, 23, 24, 26, and 28 followed the same course of disease as their counterparts treated with PBS and 1B5 mAb.

When rats were treated with R73 mAb from the time of immunization with MT and CII, the induction of both AA and CIA was blocked completely (Fig. 2, A and B).

Effect of R73 mAb on Histologic Changes in Tarsal Joints of Rats with EAA and ECIA. The effect of R73 mAb on EAA and ECIA was assessed by examining histologic changes before and after the mAb treatment period. In rats killed immediately before the treatment period, i.e., on day 14 in EAA rats (Fig. 3 A) and on day 20 in ECIA rats (Fig. 4 A), the
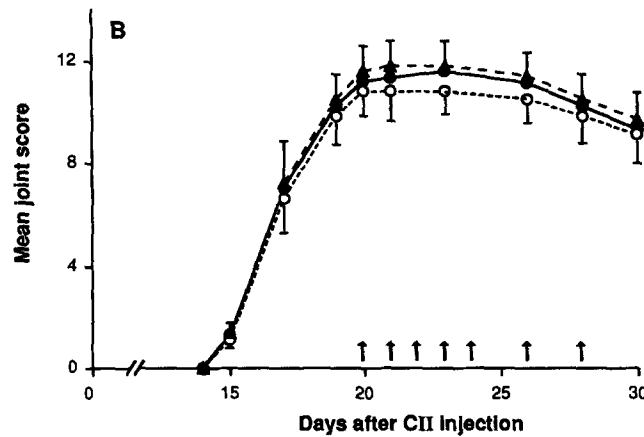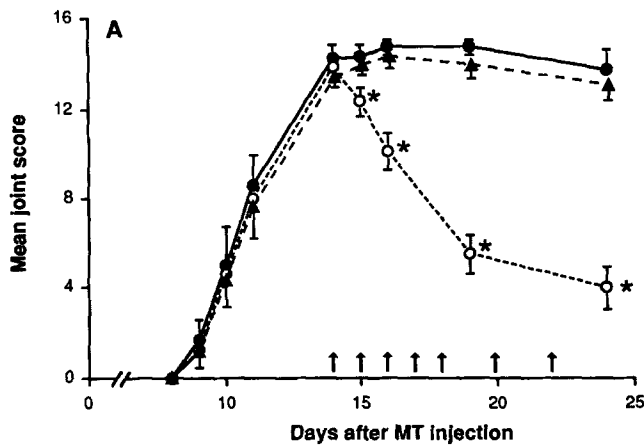
Figure 1. Comparison of the effects of R73 mAb on EAA and ECIA. PBS, 1B5 mAb, and R73 mAb were administered on days 14, 15, 16, 17, 18, 20, and 22 (*arrows*) after inoculation of MT (*A*), and on days 20, 21, 22, 23, 24, 26 and 28 (*arrows*) after immunization with CII (*B*). (●) PBS; (▲) 1B5 mAb; (○) R73 mAb. Vertical bars show SEM of five rats. R73 mAb treatment compared with PBS and 1B5 mAb treatment (student's *t* test, *$p < 0.01$).
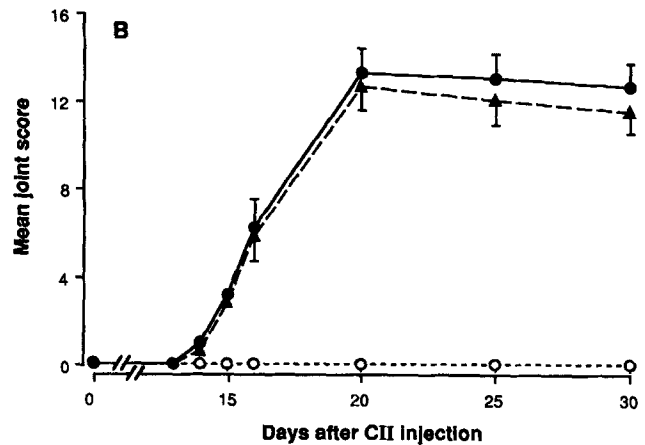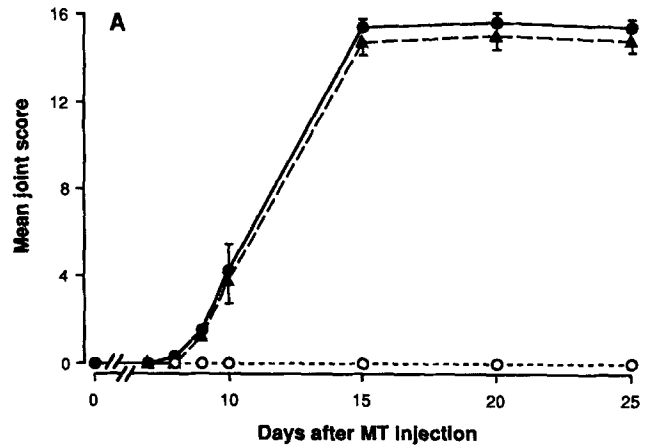

Figure 2. Prevention of the induction of AA and CIA by R73 mAb. PBS, 1B5 mAb, and R73 mAb were administered every 3 d from the time of immunization with MT (*A*) and CII (*B*) up to days 21 and 27, respectively. (●) PBS; (▲) 1B5 mAb; (○) R73 mAb. Vertical bars show SEM of five rats.

joints exhibited synovial edema with infiltration of many inflammatory cells, including neutrophils and mononuclear cells, but only minimal erosion of cartilage. When assessed after treatment, PBS- and 1B5 mAb–treated rats with EAA (day 24, Fig. 3 *B*) and ECIA (day 30, Fig. 4 *B*) had developed pronounced pannus, dense inflammatory cell infiltrate in which mononuclear cells predominated, and severe destruction of cartilage and subchondral bone. Treatment of EAA with R73 mAb suppressed markedly pannus formation and infiltration of inflammatory cells and prevented the damage of cartilage and bone (Fig. 3 *C*). In contrast, R73 mAb–treated rats with ECIA developed chronic erosive synovitis (Fig. 4 *C*) similar to that seen in animals injected with PBS and 1B5 mAb.

Effect of R73 mAb on the Percentage of α/β⁺ and CD5⁺ T Cells in Peripheral Blood in Rats with EAA and ECIA. α/β⁺ and CD5⁺ T cells in peripheral blood of rats treated with PBS, 1B5 mAb, and R73 mAb were examined on days

14, 18, and 24 in rats with EAA, and on days 20, 24, and 30 in rats with ECIA. 35–45% of leukocytes were R73⁺ and OX19⁺ before treatment and throughout treatment with PBS or 1B5 mAb irrespective of the arthritogen used (Table 1). In contrast, TCR-α/β and CD5⁺ T cells in R73 mAb–treated rats with EAA and ECIA constituted ∿5% of leukocytes.

Effect of R73 mAb on the Depletion of α/β⁺ and CD5⁺ T Cells in Synovial Tissues of Rats with EAA and ECIA. A large number of α/β⁺ and CD5⁺ T cells were present in synovial tissues of rats with EAA and ECIA treated with either PBS or 1B5 mAb on days 17 and 23, respectively. Typical findings are shown in Fig. 5 *A*. There was no significant difference in the positive cell numbers between EAA and ECIA. In contrast, there was a marked reduced number of synovial tissue α/β⁺ and CD5⁺ T cells in R73 mAb–treated rats with EAA and ECIA (Fig. 5 *B*). Cells in synovial tissues as well as in peripheral blood from R73 mAb–treated rats were not stained with the secondary antibody (not shown).
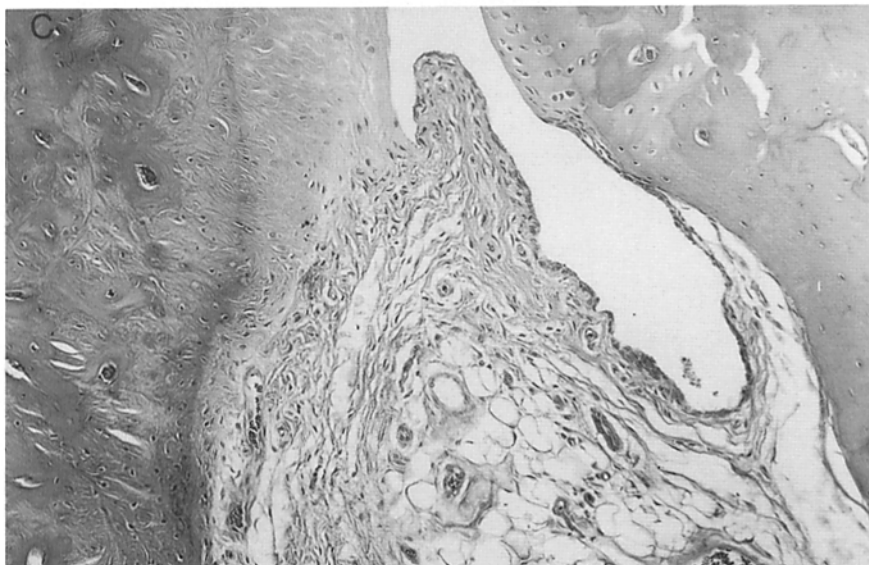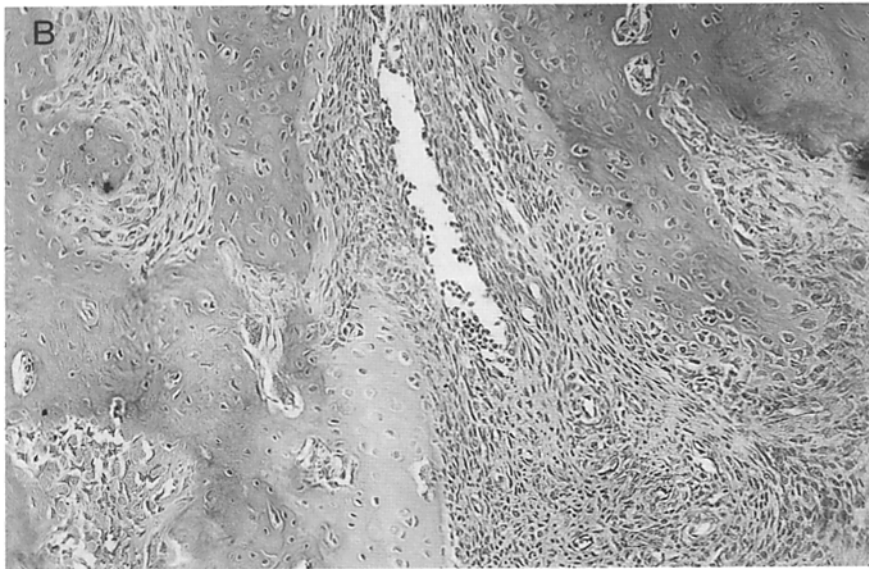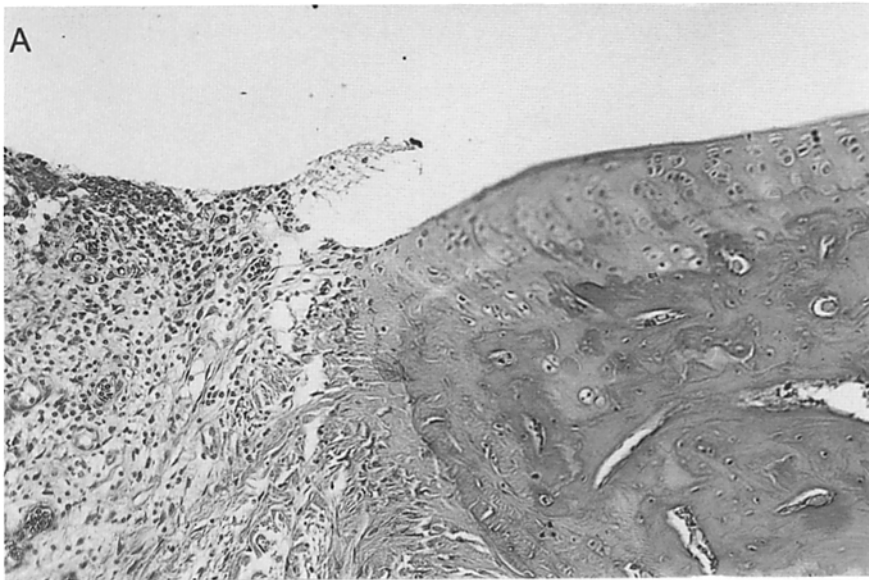
Figure 3. Histologic changes in tarsal joints of rats with EAA after treatment with R73 mAb. Tarsal joints of rats with EAA were examined immediately before commencement of the R73 mAb treatment period on day 14 (*A*) and after treatment with PBS or 1B5 mAb (*B*) and with R73 mAb (*C*) on day 24. H&E stained, ×100.
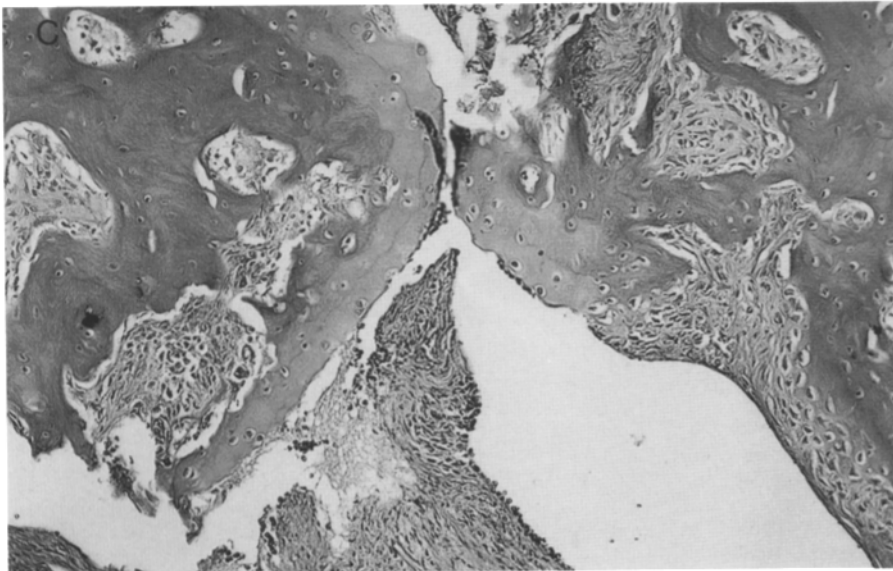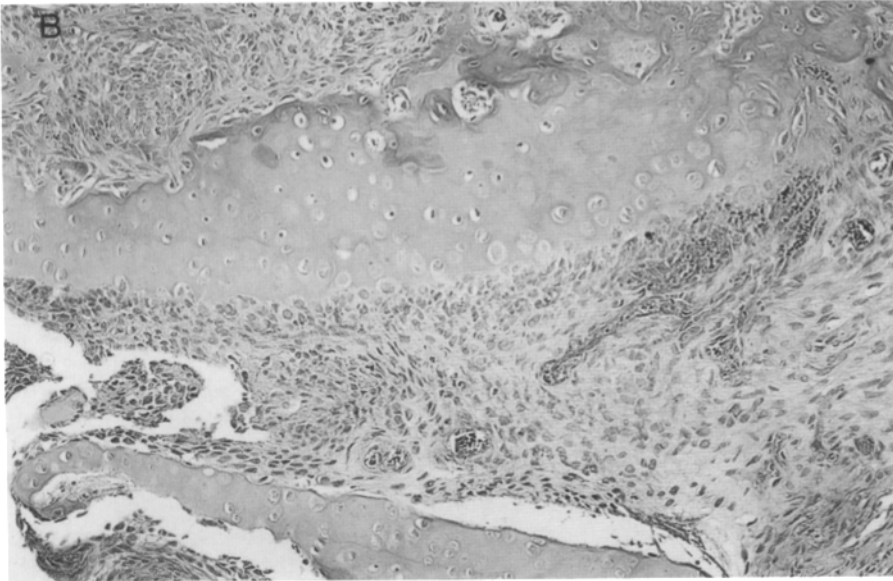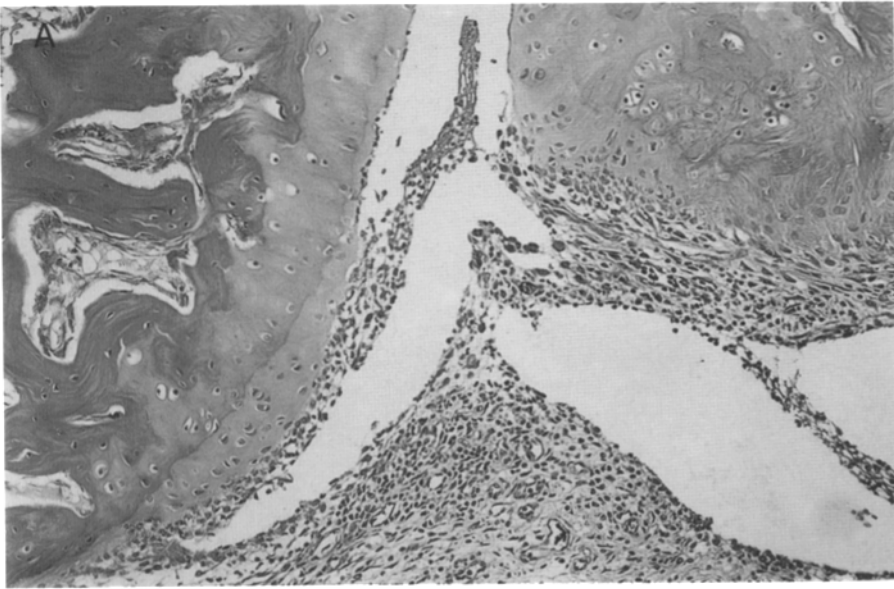
Figure 4. Histologic changes in tarsal joints of rats with ECIA after treatment with R73 mAb. Tarsal joints of rats with ECIA were examined immediately before commencement of the R73 mAb treatment period on day 20 (*A*) and after treatment with PBS or 1B5 mAb (*B*), and with R73 mAb (*C*) on day 30. H&E stained, ×100.

Table 1. *Depletion of α/β⁺ and CD5⁺ T Cells by R73 mAb in Peripheral Blood in Rats with EAA and ECIA*

Group	Day	α/β⁺ leukocytes			CD5⁺ leukocytes		
		PBS	1B5 mAb	R73 mAb	PBS	1B5 mAb	R73 mAb
		%			%		
	14	33 ± 2.7	35 ± 2.3	33 ± 3.1	36 ± 3.2	35 ± 2.6	36 ± 3.6
EAA	18	35 ± 3.0	37 ± 2.8	2 ± 2.7*	34 ± 2.8	35 ± 3.0	3 ± 3.1*
	24	38 ± 3.3	40 ± 3.1	6 ± 3.0*	41 ± 3.5	42 ± 3.3	6 ± 3.6*
	20	43 ± 4.0	40 ± 3.2	42 ± 4.1	41 ± 3.5	43 ± 3.5	42 ± 3.8
ECIA	24	41 ± 3.8	40 ± 2.8	3 ± 3.3*	45 ± 4.4	40 ± 3.2	3 ± 2.9*
	30	45 ± 4.2	44 ± 3.0	5 ± 4.9*	45 ± 4.0	42 ± 3.5	7 ± 3.4*

PBS, 1B5 mAb, and R73 mAb were administered on days 14, 15, 16, 17, 18, 20, and 22 after inoculation of MT, and on days 20, 21, 22, 23, 24, 26, and 28 after immunization with CII. The percentages of α/β⁺ and CD5⁺ T cells in peripheral leukocytes from rats with EAA and ECIA were determined by preparing blood smears immediately before the scheduled injection of R73 mAb on the days indicated. Values are expressed as mean ± SEM of five rats. R73 mAb treatment compared with PBS and 1B5 mAb treatment (student's *t* test, *p < 0.01).

Effect of R73 mAb on DTH Responses to MT and CII in Rats with EAA and ECIA, Respectively. To examine the effect of α/β⁺ T cell depletion on cell-mediated immune responses, the ear DTH responses to MT and CII in R73 mAb-treated rats with EAA and ECIA, respectively, were determined. As shown in Table 2, R73 mAb-treated rats showed markedly reduced DTH responses to the respective immunizing agents compared with their PBS- and 1B5 mAb-treated counterparts.

Effect of R73 mAb on Production of Antibodies to CII in Rats with ECIA. To determine whether R73 mAb treatment affected established antibody levels, anti-CII antibody titers were determined in ECIA rats. The results showed that there was no significant difference in titers of antibodies to CII on days 20, 25, and 30 after immunization with CII between PBS-, 1B5 mAb- and R73 mAb-treated rats (Table 3).

Discussion

A role for T cells in the induction of AA and CIA has been established (6–9). However, the influence of T cells in maintaining established arthritis in these models has not been critically examined. In the present studies, arthritogen-specific cell-mediated immune responses were reduced markedly in R73 mAb-treated rats with EAA and ECIA, as evidenced by significantly suppressed DTH responses to MT and CII, respectively. However, α/β⁺ T cells may exert a crucial sustaining effect on the course of EAA, but not in ECIA, since the depletion of α/β⁺ T cells by R73 mAb against TCR-α/β markedly suppressed EAA, but did not affect the progression of ECIA.

The mechanism of progression of ECIA is not clear at present. Antibodies to CII may be a potentially critical factor after the disease is established. Polyarthritis can be transferred passively to naive recipient rats with anti-CII antibodies (16), although the disease is transient and a role for the humoral

Table 2. *Effect of R73 mAb on the DTH Responses to MT and CII in Rats with EAA and ECIA, Respectively*

Group	Increase in ear thickness		
	PBS	1B5 mAb	R73 mAb
	× 10⁻² mm		
EAA	72 ± 6.8	66 ± 5.7	15 ± 3.0*
ECIA	101 ± 7.5	91 ± 8.3	22 ± 3.7*

PBS, 1B5 mAb, and R73 mAb were administered on days 14, 15, 16, 17, 18, 20, and 22 after inoculation of MT, and on days 20, 21, 22, 23, 24, 26, and 28 after immunization with CII. The ear DTH responses to MT in rats with EAA and to CII in rats with ECIA were tested on days 18 and 24, respectively, as described in Materials and Methods. Values are expressed as mean ± SEM of five rats. R73 mAb treatment compared with PBS and 1B5 mAb treatment (student's *t* test, *p < 0.01).

Table 3. *Effect of R73 mAb on the Production of Antibodies to CII in Rats with ECIA*

	Anti-CII antibody titer		
Day	PBS	1B5 mAb	R73 mAb
	− log₂		
20	10.5 ± 0.43	10.2 ± 0.41	9.8 ± 0.33
25	11.4 ± 0.42	10.8 ± 0.37	10.6 ± 0.24
30	11.2 ± 0.51	10.4 ± 0.45	10.6 ± 0.36

PBS, 1B5 mAb, and R73 mAb were administered on days 20, 21, 22, 23, 24, 26, and 28 after immunization with CII. Anti-CII antibody titers were determined by an ELISA on the days indicated. Values are expressed as mean ± SEM of five rats.
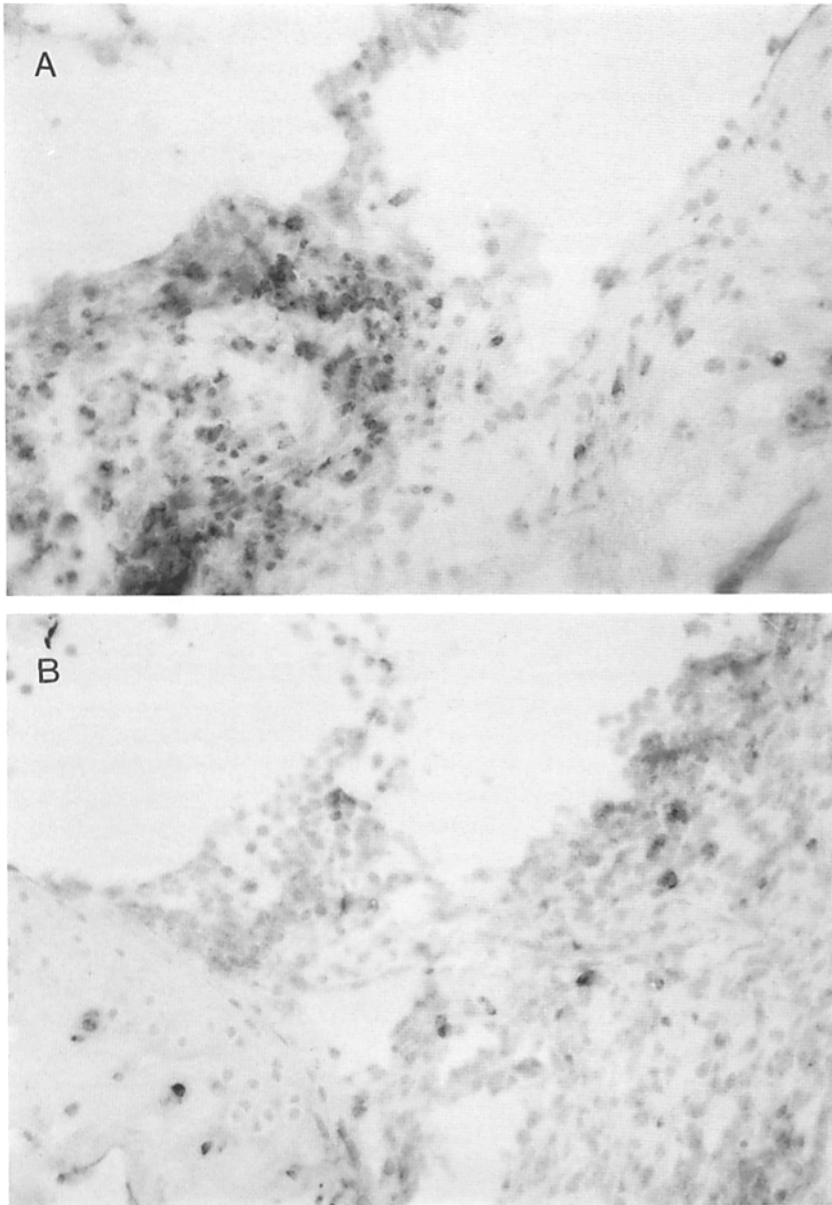
Figure 5. Depletion of α/β^+ and $CD5^+$ T cells in synovial tissues of rats with EAA and ECIA by R73 mAb. PBS, 1B5 mAb, and R73 mAb were administered on days 14–17, and on days 20–23 after immunization with MT and CII, respectively. 7 h after the last dose, α/β^+ and $CD5^+$ T cells in tarsal joints of rats with EAA and ECIA were detected by the APAAP method. (A) PBS- or 1B5 mAb–treated rats with ECIA; (B) R73 mAb–treated rats with ECIA ($\times 200$). Essentially similar findings were obtained with EAA rats.

response beyond the induction phase of CIA can not be inferred. There has been no published demonstration that AA can be transferred with serum from MT-primed rats. We have failed to achieve adoptive transfer of AA to syngeneic naive recipient rats with serum from rats with EAA, but have induced transient polyarthritis in rats by adoptive transfer with serum from CII-primed animals (our unpublished data). Established anti-CII antibody levels in rats with ECIA were not affected by treatment with R73 mAb, thus allowing a contribution by anti-CII antibodies to the persistent destructive arthritis in R73 mAb–treated animals.

We have shown previously (17, 18) and also in the part of the present studies that rats treated with R73 mAb from the time of immunization with MT and CII do not develop polyarthritis. The present studies were designed to evaluate the role of T cells in the mediation of established disease in these two models of arthritis. The findings suggest that AA is T cell dependent in both induction and maintenance of disease, while T cells have a role in induction of CIA, but may not be required for maintenance of the established disease. T cells are needed to induce the humoral response to CII since anti-CII antibody production is T cell dependent (19), but once this response is established, T cells may not be required to sustain antibody level, at least in the short term. Thus, ECIA might be antibody dependent, but not dependent on the continuing participation of T cells beyond the induction phase.

A large number of T cells are present in inflamed synovium of rats with AA (20) and CIA (21). The present immunohistological investigations confirmed the infiltration of many α/β^+ and $CD5^+$ T cells in synovial tissues in the both forms of arthritis. T cells are also a prominent cell in

synovial tissues of patients with RA (1-3). However, the presence of T cells does not necessarily implicate a direct role for T cells in maintaining existing arthritis as shown by the difference in effect of the anti-TCR-α/β mAb on EAA and ECIA in the present studies. After intraperitoneal injection of R73 mAb, the mAb can be expected to enter the inflamed synovium and bind TCR-α/β expressed on synovial α/β^+ T cells of rats with either EAA or ECIA. The results indicating that EAA was suppressed significantly within 24 h after administration of R73 mAb suggest a direct effect of the mAb on arthritogenic T cells in synovial tissues. In addition, the effect of R73 mAb therapy on the recruitment of T cells into synovium is suggested by the observed depletion of synovial α/β^+ and CD5$^+$ T cells. To our knowledge, this is the first demonstration that a mAb therapy for arthritis depletes inflamed synovial tissue T cells.

The proportionate depletion of CD5$^+$ and R73$^+$ T cells in peripheral blood as well as synovial tissues in R73 mAb-treated rats excludes the possibility that modulation of TCR-α/β by R73 mAb might render α/β^+ T cells undetectable without causing depletion. Cells coated with R73 mAb in vivo could not be detected in either peripheral blood or synovial tissues from R73 mAb-treated rats with EAA and ECIA by application of the secondary antibody and revealing agents. R73 mAb is of the IgG1 isotype and therefore should not fix complement. A relatively weak complement-fixing IgG2a mAb against Thy-1.2 efficiently eliminated Thy-1.2 cells from the blood of mice in vivo and was shown to opsonize Thy-1.2-bearing cells for phagocytosis in vitro (22). Therefore, it seems likely that opsonization and clearance by the reticuloendothelial system is the mechanism for the T cell depletion caused by this mAb. A similar mechanism could account for the T cell-depleting effect of R73 mAb.

R73 mAb depletes specifically α/β^+ T cells, but does not affect γ/δ^+ T cells (10). γ/δ^+ T cells respond to MT (23) and heat-shock proteins (24), and have been found in syno-

vial fluid in RA (25). Accordingly, a role for γ/δ^+ T cells in RA and animals models of arthritis such as EAA and ECIA needs to be considered. In the case of ECIA, the lack of effect of α/β^+ T cell depletion by R73 mAb allows the possibility that γ/δ^+ T cells could be contributing to the maintenance of ECIA. A role for γ/δ^+ T cells is less likely in EAA, which is markedly suppressed by R73 mAb treatment. However, it remains possible that γ/δ^+ T cells might have a role in the presence of α/β^+ T cells. A more precise definition of the role of γ/δ^+ T cells in these models of polyarthritis awaits the development of mAbs against the TCR-γ/δ that can be used to assess the effect of γ/δ^+ T cell depletion on disease induction and expression.

Both AA (4) and CIA (5) resemble RA in many important respects. However, it is not clear which model more reliably reflects the pathological process occurring in established RA. mAbs against CD4 (26, 27) and IL-2R (28) have recently been shown to have a beneficial effect on RA, although not all subjects have responded and the number of patients treated with these antibodies is small. These studies suggest that T cells play a central role in at least some cases of established RA as occurs in EAA. On the other hand, an important involvement of the humoral response in RA has also been argued. For instance, a large amount of autoreactive Ig is produced by rheumatoid synovium (29) and the low levels of complement activity in rheumatoid synovial fluid suggests consumption of complement by local antigen-antibody complexes (30). Further evaluation of treatment with anti-TCR mAbs should provide further understanding of the key pathogenic events in established RA, including better definition of the respective roles of humoral and cell-mediated immune responses. Indeed, specific anti-T cell reagents could allow more precise categorization of RA into subtypes defined by their apparent dependence upon different T cell subpopulations.

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