Rheumatoid keratolysis: A series of 40 eyes

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PURPOSE. *Rheumatoid keratolysis (RK) is a rare but a serious cause of ocular morbidity in rheumatoid patients. The aim of this study was to analyze the presenting features, the subsequent treatment, and the outcome of patients with RK in the authors' department.*
METHODS*. A retrospective study was undertaken of all patients with a diagnosis of RK at Bristol Eye Hospital between January 1987 and June 2002.*
RESULTS*. Forty eyes of 38 patients were identified in total. The mean age at presentation was 70 years. The mean duration of rheumatoid arthritis at presentation was 15 years. Most (22, 55%) ulcers were peripheral. Three patients (8%) developed RK within a month of cataract surgery. Out of the 19 patients who did not have a further RK, 11 were immunosuppressed. A total of 37 grafts were performed on 26 eyes. Twenty-two grafts (59%) failed. Immunosuppression increased the chance of anatomical success following penetrating keratoplasty. Infection was identified as a cause of graft failure for immunosuppressed patients in the postoperative period. Nine patients had reversible side effects from immunosuppressant treatment. Four eyes (10%) had to be surgically removed and a further 10 (25%) had severe visual loss (visual acuity less than 6/60). Eleven of the 38 patients subsequently died (29% mortality).*
CONCLUSIONS*. Although the visual prognosis is often poor, surgical preservation of the eye can be achieved by penetrating keratoplasty and systemic immunosuppression. With careful observation and regular monitoring, immunosuppressive medication appears to be safely tolerated in this group of patients. (Eur J Ophthalmol 2006; 16: 791-7)*

KEY WORDS. *Rheumatoid disease, Keratolysis, Immunosuppression*

INTRODUCTION

Rheumatoid arthritis is a symmetric inflammatory polyarthritis that has preponderance for peripheral joints. It affects between 1 and 3% of the general population (1-3). Extra-articular features are present in 25% of patients (2). Ocular manifestations include keratoconjunctivitis sicca, episcleritis, and scleritis. Rheumatoid keratolysis (RK) is rare but a serious cause of ocular morbidity (4). RK refers to a destructive inflammation of the corneal stroma. Although an immune-mediated inflammation plays a major part, keratoconjunctivitis sicca with an unstable corneal ep-

ithelium and infection due to deficient surface immunity may also contribute. Several factors cause production of degrading collegenases and matrix metalloproteases by the corneal epithelium. Deposition of immune complexes in the limbal vessels results in activation of complement and chemotaxis of inflammatory cells (3).

There have been only a handful of series documenting the presenting features and outcome of RK (5-7). The aim of this study was to analyze the presenting features, the subsequent treatment, and the outcome of rheumatoid patients with keratolysis within our department.

METHODS

All patients with a diagnosis of RK at Bristol Eye Hospital between January 1987 and June 2002 were included. This was done by searching for patients with corneal ulceration or rheumatoid arthritis from ward admission books and from local Hospital Episode Statistics (HES). Only patients with a definite history of rheumatoid arthritis were included. The following factors were analyzed: patient age and sex, affected eye (right, left, or both), past ocular history, duration of rheumatoid arthritis, characteristics of the ulcer, systemic and topical treatment at presentation, subsequent treatment, and final outcome.

Past ocular history

A history of dry eye or signs of keratoconjunctivitis sicca were noted (low tear film meniscus, reduced tear break-up time, central punctate keratopathy, or positive Schirmer's test ≤ 10 mm). A past history of scleritis and any evidence of previous RK (signs of old thinning or documented previous melt) were recorded. The date of any recent ocular surgery was noted as well as any significant lid abnormality (blepharitis, trichiasis, ectropion, entropion).

Ulcer characteristics

Ulcer characteristics were described in terms of size, location (limbal, peripheral, paracentral, and central), by approximate percentage of stromal thinning, and by the presence of perforation. This information was gathered from drawings in the notes and from any photographs that were available.

Treatment

Topical treatment (steroids, antibiotics, or lubricants) and systemic treatment (steroids, immunosuppressants) prior to presentation were recorded as well as the subsequent treatment. For the purpose of this study, and for ease of comparison, any patient who was on 20 mg or more of prednisolone or on an alternative immunosuppressant agent after presentation was classified as "immunosuppressed". Any other patient was classified as "non-immunosuppressed". This arbitrary division was chosen because patients in general were either on low doses (5–10 mg prednisolone) or high dose (more than 40 mg prednisolone, or alternative immunosuppressant) after their RK was diagnosed. All side effects of treatment were documented. A note was made of surgical procedures performed to seal a perforation or impending perforation. Penetrating keratoplasties (PKP) were done for either tectonic or visual reasons.

Outcome

Outcomes at the final available follow-up were measured in terms of a fresh RK after the initial episode, final visual acuity, surgical loss of an eye, and mortality. Final visual acuity was measured in terms of best-corrected (i.e., glasses, contact-lens, or pinhole). A fresh RK was defined as a recurrence of keratolysis after the initial episode resolved. Infective keratitis was defined by signs that made infection likely (pain, dense infiltrate, anterior chamber activity including a hypopyon) or growth of organisms on corneal scrape. A surgical procedure to seal a perforation was defined as anatomically successful if no other surgical procedure was needed subsequently. Graft failure was defined as irreversible loss of graft clarity. The cause of each graft failure was documented. The immunosuppressant status of the patient at the time of each graft failure was noted.

RESULTS

Thirty-eight patients were identified in total. All of these patients had a reliable history of rheumatoid arthritis and presented with keratolysis. In total, 40 eyes were analyzed. Of these, 23 involved the right eye, 15 involved the left eye, and 2 patients presented with bilateral simultaneous RK. The mean follow-up time was 3 years (range 1 month–12 years).

Demographic data

The majority of patients were female (22, 58% versus 16, 42% males). The mean age at presentation was 70 years (median = 71 years, range = 50–93). The mean duration of rheumatoid arthritis at presentation was 15 years (median = 20 years, range = 6–60 years).

Past ocular history

Twenty-seven patients (71%) had clinical evidence of dry eye. Fourteen of these were on topical lubricants in the affected eye at the time. Half (n = 19, 50%) of the patients who presented with a RK had evidence of a previous RK in the affected or fellow eye. Only one patient's keratolysis was preceded by scleritis, although 35 (88%) eyes had concurrent limbal inflammation. Three patients (8%) presented within a month of cataract surgery.

Ulcer characteristics

Twenty-two (55%) ulcers were peripheral, 10 (25%) were paracentral, 7 (17%) were central, and 1 (3%) ulcer was limbal. Twenty (50%) eyes presented with a perforation and 9 (23%) more subsequently perforated. Of the 17 (43%) ulcers that were either paracentral or central, 7 (18%) patients had raised inflammatory markers and a further 5 (13%) had signs of limbal inflammation, i.e., 12 (30%) of these ulcers had some evidence of a vasculitic component. The duration of new symptoms at presentation ranged from 1 day to 5 months (mean 29 days). Figure 1 shows one eye in our series which developed a perforated graft due to a recurrent keratolysis.

Immunosuppression

Steroids were used most commonly (29, 76% patients). Other immunosuppressants used were azathioprine, methotrexate, and pulsed cyclophosphamide (Tab. I). Side effects encountered from immunosuppressive treatment are shown in Table II. Some patients were on more than one mode of treatment. All 9 (24%) of these patients had their treatment changed as a result of these adverse effects. These effects were transient and regressed following the change of treatment.

Subsequent course

Twenty-one (53%) eyes developed a fresh RK after the initial presentation. Of the 19 (48%) patients who did not have a further RK, 11 (28%) were immunosuppressed. Seventeen eyes developed infective ker-

atitis after the first RK. Of these 8 (20%) were on systemic treatment.

Penetrating keratoplasty

A total of 37 grafts were performed on 26 eyes. Seven patients received multiple grafts. Twenty-nine (78%) of these were done to maintain the integrity of the eye, while 8 (22%) were done for visual reasons. Twenty-two grafts (59%) failed. Ten (45%) failed due to infection; 9 (41%) due to persistent keratolysis; 2 (9%) due to rejection; and 1 (5%) due to late endothelial failure. Overall, immunosuppression was associated with a trend toward a higher chance of graft survival, although this did not reach statistical significance (p=0.33, log-rank chi-square = 0.94). However, the probabili-

TABLE I - RANGE OF IMMUNOSUPPRESSANTS USED

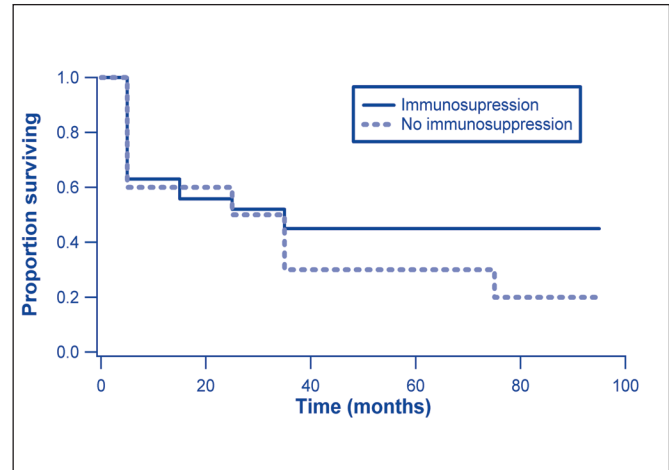| Immunosuppressive	No. (%) of patients*
Oral steroids	29 (40)
IV pulse steroids	6 (8)
Azathioprine, AZA	18 (25)
Methotrexate, MXT	12 (17)
Cyclophosphamide, CXP	6 (8)
Cyclosporin A, CSA	1 (1)
Total	72*

*Some patients were on more than one treatment.

TABLE II - SIDE EFFECTS OF IMMUNOSUPPRESSANT TREATMENT

Immunosuppressant Frequency	Side effect	
Steroids	Collapse with IV methylprednisolone	1
	Steroid induced diabetes	2
	Chest infection	1
Methotrexate	Pancytopenia	1
	Pulmonary toxicity	2
Cyclosporin A	Abnormal liver function	1
Azathioprine	General unwell feeling/malaise	1
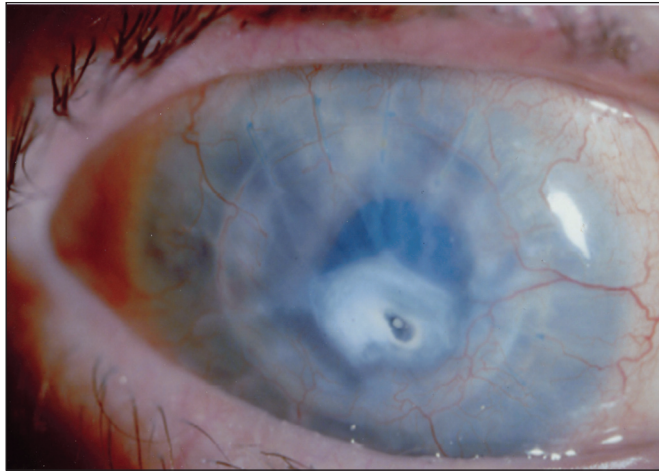
Fig. 1 - *One eye in the series. The picture shows a perforated graft resulting from a paracentral rheumatoid keratolysis.*

Fig. 2 - *Graft (PKP) survival in patients with rheumatoid keratolysis who received immunosuppressant therapy (black line) versus those patients who did not receive immunosuppressant treatment (grey line), p=0.33, log-rank chi-square = 0.94.*

ty of graft survival beyond 3 years was doubled if the patient was on immunosuppressant treatment (Fig. 2). For the immunosuppressed group, 9 (24%) grafts failed within the first 10 months. Two grafts failed due to persistent keratolysis, 1 rejected, and 6 of these failed due to infection: 2 developed endophthalmitis after combined PKP/cataract extraction; in 2 patients infective keratitis followed a suture abscess. In two patients no cause of infection could be identified.

Other surgical procedures

Glue was used in 12 eyes. Other surgical procedures were not used commonly. Conjunctival recession was performed in 4 eyes and 3 eyes received lamellar keratoplasty.

Anatomic success

Of the 29 PKPs done for tectonic reasons, no further surgical intervention was needed in 23 cases (79% anatomic success). Gluing achieved anatomic success only half of the time (6 out of 12). PKP was associated with a higher rate of anatomical success than gluing. It is unfair, though, to directly compare these two methods as they are often used in different situations. At any time postoperatively, the probability of anatomical success of PKP was higher in patients who were im-
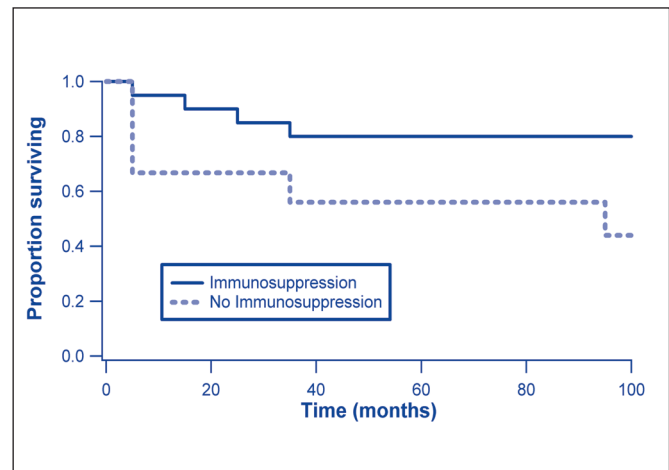
Fig. 3 - *PKP anatomic survival in rheumatoid keratolysis for patients who received immunosuppressant treatment (black line) versus those who did not (grey line), p=0.04, log-rank chi-square = 4.40.*

munosuppressed (Fig. 3). This was statistically significant (p=0.04, log-rank chi-square = 4.40).

Use of topical steroid

The use of topical steroid in immunosuppressed (16 patients) and non-immunosuppressed (5 patients) patients was considered separately. In each case, the use of topical steroid was not associated with a higher rate of fresh keratolysis (Fisher exact test p=1.0
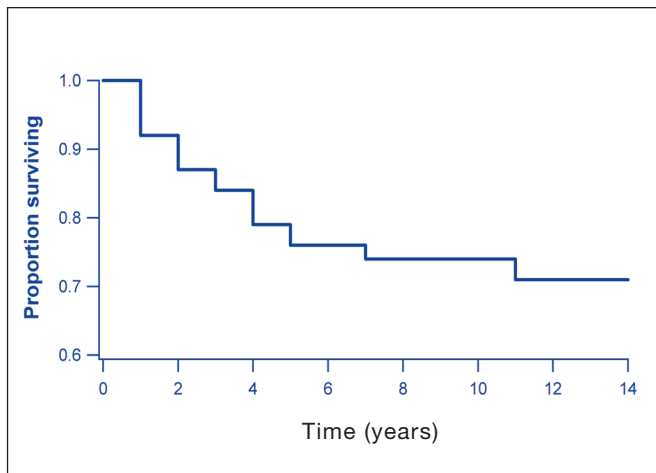
Fig. 4 - *Mortality of patients with rheumatoid keratolysis.*

and p=0.7, respectively). These small numbers, in a retrospective context, are not conclusive.

Final visual outcome

Four eyes (10%) had to be surgically removed (3 eviscerated and 1 enucleated) and a further 10 (25%) had severe visual loss (i.e., visual acuity less than 6/60). Of these, 3 (8%) had significant other ocular comorbidity (1 ischemic central retinal vein occlusion, 2 dense cataract). Ten eyes (25%) achieved final visual acuity of 6/12 or better, 16 (40%) had final vision between 6/12 and 6/60.

Mortality

Eleven of the 38 patients subsequently died (29% mortality) (Fig. 4). Five of these (13%) had been on immunosuppressant therapy. Out of these 5, who had been immunosuppressed following their RK, 4 had a recurrent RK. This suggests they may have been undertreated. Nine of the patients (24%) died within 5 years of initial presentation. There was no difference (t=0.19, p=0.86) between the mean age at death of patients who were immunosuppressed (75 ± 7 years) and those who were not (76 ± 10 years).

DISCUSSION

Inspection of the results from this study suggests the following. Firstly, rheumatoid keratolysis is an aggressive condition with a poor visual prognosis and high associated mortality. Secondly, the chance of graft survival and anatomic survival can be increased with systemic immunosuppressant therapy. Finally, clinicians should be vigilant about the risk of graft infection in the early postoperative period.

In this study, 4 (10%) eyes were surgically lost (3 eviscerated and 1 enucleated) and an additional 10 (25%) patients had severe visual loss. Poor vision often results from a thinned, hazy, perforated, or vascularized cornea. The visual outcome of RK is known to be poor (3-5, 8-11). Messmer and Foster documented a final visual acuity of less than 20/400 in 26% of patients with peripheral keratitis (4), while Palay et al reported this figure to be 47% (10). The latter only considered rheumatoid patients who had received penetrating keratoplasty, mostly for corneal perforation or descemetocele. It is likely this group had more aggressive disease and this may explain the poorer final visual acuity.

The 5-year mortality of patients after presentation in our series was 24%. This is consistent with other studies, which report mortality between 9.4 (11 years) to 45.5% (3 years) for rheumatoid scleritis (12, 13). Rheumatoid patients have reduced life expectancy due to the presence of systemic vasculitis (14). In Foster et al's study, 7 out of 20 patients died from vascular-related deaths over a 10-year period (15). In another study of patients with RK, more than half of the patients died within 5 years of receiving their first graft (10). At postmortem examination, more than 30% of rheumatoid patients have evidence of systemic angiitis (16). In a study of nine seropositive rheumatoid patients, one patient died within 1 month of RK diagnosis (7).

Our results confirm previous reports of increased graft survival with immunosuppressant therapy (5, 10) and that PKP can be anatomically successful in patients with rheumatoid arthritis (9). Furthermore, analysis of our data suggests that the chance of anatomic success is significantly higher in rheumatoid patients who are immunosuppressed. In this study 78% of grafts were done to maintain the integrity of the eye. It would seem reasonable, therefore, to use anatomic success as a primary outcome measure for these cases. Several investigators have found that chemotherapy in combination with surgery can maintain the

integrity of the globe (9, 11).

Only nine patents had side effects from immunosuppressant treatment, all of which were reversible on withdrawal of the drug. One study reported mild side effects in 11 (out of 16) patients treated with systemic immunosuppressant therapy, all of which were reversible and disappeared on withdrawing the drug (4). These findings would suggest that such therapy can be tolerated in this group of patients with careful monitoring. Fear of adverse drug reactions is a potential cause of withholding systemic immunosuppressant therapy and subsequent poor visual outcome.

Infection was identified as a significant cause of graft failure especially for immunosuppressed patients in the early postoperative period (six patients, two of whom developed endophthalmitis after combined PKP/cataract extraction). These patients may be at high risk of infection because of systemic immunosuppression, deficient surface immunity, a lack of surface tear film with epithelial instability, and the use of topical steroid medication. Careful monitoring for signs of infection and prompt antibiotic and topical lubrication in the postoperative phase may help to reduce the incidence of this complication.

This study is confounded by a number of factors. First, our classification of immunosuppression, i.e., patients being on 20 mg of prednisolone or more or an alternative immunosuppressive agent, was arbitrary. Secondly, it is possible that all the cases analyzed here were not true cases of RK. Some studies have classified RK as peripheral necrotizing and central non-necrotizing based on the presumed etiology (5, 12). These two entities represent ends of a disease spectrum and RK is probably the result of a complex interaction of both vasculitic and non-vasculitic factors. We specifically excluded corneal pathology that was predominantly due to pathology other than rheumatoid disease (e.g., marginal keratitis, contact lens related ulcers). In our series, 43% of ulcers were central and paracentral. In most of these (71%), there was evidence of limbal inflammation or raised serum inflammatory markers, thus indicating a possible vasculitic component.

There is some evidence that cell-mediated immune mechanisms play a role in paracentral ulcers in rheumatoid ulceration, and topical cyclosporin has been reported as a successful treatment for these (17, 18).

This study suffers from the usual constraints of retrospective work, namely: changing medical and surgical treatment over time, differing surgical and medical management among different physicians, and lack of detailed information regarding specific outcome measures in case notes. In view of the lack of prospective evidence for the optimal treatment of RK and the emergence of newer medical and surgical treatments (19-21), there is a need for a randomized controlled prospective study to evaluate the optimal treatment for RK.

CONCLUSIONS

RK is an aggressive condition with a high morbidity and associated mortality. Although the visual prognosis is often poor, surgical preservation of the eye can be achieved by penetrating keratoplasty and systemic immunosuppression. Clinicians should be vigilant about the early risk of graft infection in immunosuppressed patients. Inadequate immunosuppression is likely to be a cause of poor visual outcome and graft survival. With careful observation and regular monitoring, immunosuppressant medication appears to be safely tolerated in this group of patients.

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REFERENCES

1. Buckley CD. Science, medicine, and the future. Treatment of rheumatoid arthritis. BMJ 1997; 315: 236-8.
2. Koffler D. The immunology of rheumatoid diseases. Clin Symp 1979; 31: 1-36.
3. Messmer EM, Foster CS. Vasculitic peripheral ulcerative keratitis. Surv Ophthalmol 1999; 43: 379-96.
4. Messmer EM, Foster CS. Destructive corneal and scleral disease associated with rheumatoid arthritis. Medical and surgical management. Cornea 1995; 14: 408-17.
5. Bernauer W, Ficker LA, Watson PG, Dart JK. The management of corneal perforations associated with rheumatoid arthritis. An analysis of 32 eyes. Ophthalmology 1995; 102: 1325-37.
6. Foster CS. Immunosuppressive therapy for external ocular inflammatory disease. Ophthalmology 1980; 87: 140-50.
7. Squirrel DM, Winfield J, Amos RS. Peripheral ulcerative keratitis 'corneal melt' and rheumatoid arthritis: a case series. Rheumatology 1999; 38: 1245-8.
8. Jifi-Bahlool H, Saadeh C, O'Connor J. Peripheral ulcerative keratitis in the setting of rheumatoid arthritis: treatment with immunosuppressive therapy. Semin Arthritis Rheum 1995; 25: 67-73.
9. Raizman MB, Sainz de la Maza M, Foster CS. Tectonic keratoplasty for peripheral ulcerative keratitis. Cornea 1991; 10: 312-6.
10. Palay DA, Stulting RD, Waring GO 3rd, Wilson LA. Penetrating keratoplasty in patients with rheumatoid arthritis. Ophthalmology 1992; 99: 622-7.
11. Wiezorrek R, Bialasiewicz AA, Engelmann K, Grasedyck K, Richard G. Necrotizing keratitis in chronic polyarthritis. Combined immunosuppressive and surgical therapy. Ophthalmologe 1998; 95: 619-24.
12. Sainz de la Maza M, Foster CS, Jabbur NS. Scleritis associated with rheumatoid arthritis and with other systemic immune-mediated diseases. Ophthalmology 1994; 101: 1281-6.
13. McGavin DD, Williamson J, Forrester JV, et al. Episcleritis and scleritis. A study of their clinical manifestations and association with rheumatoid arthritis. Br J Ophthalmol 1976; 60: 192-226.
14. Vandenbroucke JP, Hazevoet HM, Cats A. Survival and cause of death in rheumatoid arthritis: a 25-year prospective followup. J Rheumatol 1984; 11: 158-61.
15. Foster CS, Forstot SL, Wilson LA. Mortality rate in rheumatoid arthritis patients developing necrotizing scleritis or peripheral ulcerative keratitis. Effects of systemic immunosuppression. Ophthalmology 1984; 91: 1253-63.
16. Suzuki A, Ohosone Y, Obana M, et al. Cause of death in 81 autopsied patients with rheumatoid arthritis. J Rheumatol 1994; 21: 33-6.
17. Kervick GN, Pflugfelder SC, Haimovici R, Brown H, Tozman E, Yee R. Paracentral rheumatoid corneal ulceration. Clinical features and cyclosporine therapy. Ophthalmology 1992; 99: 842.
18. Gottsch JD, Akpek EK. Topical cyclosporin stimulates neovascularization in resolving sterile rheumatoid central corneal ulcers. Trans Am Ophthalmol Soc 2000; 98: 81-7.
19. Thomas JW, Pfugfelder SC. Therapy of progressive rheumatoid arthritis-associated corneal ulceration with infliximab. Cornea 2005; 24: 742-4.
20. Solomon A, Meller D, Prabhasawat P, et al. Amniotic membrane grafts for nontraumatic corneal perforations, descemetoceles, and deep ulcers. Ophthalmology 2002; 109: 694-703.
21. Hicks S, Demers PE, Brunette I, La C, Mabon M, Duchesne B. Amniotic membrane transplantation of corneal ulcers and perforations: a review of 33 cases. Cornea 2005; 24: 369-77.