Case Report

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Adrenocorticotropic hormone gel in patients with refractory rheumatoid arthritis: a case series

While many patients with rheumatoid arthritis respond to treatment with disease-modifying antirheumatic drugs, some patients have refractory disease. The mechanism of action of adrenocorticotropic hormone (ACTH) gel and its direct action on melanocortin receptors is thought to result in steroid-independent anti-inflammatory and immunomodulatory effects, in addition to steroidogenic effects. ACTH gel may provide efficacy for patients who previously failed treatment with prednisone or disease-modifying antirheumatic drugs. In this case series, we report five patients with refractory rheumatoid arthritis on ACTH gel who have failed up to five previous treatments. In these patients, ACTH gel provided improvements in inflammatory markers and/or patient-reported symptoms in each case.

Keywords: adrenocorticotropic hormone • refractory rheumatoid arthritis • rheumatoid arthritis biologic failures • rheumatoid arthritis treatment

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Despite progress in pharmacotherapy for rheumatoid arthritis (RA) and numerous available treatment options, a significant need exists for effective and tolerable treatments, particularly for patients with refractory disease [1]. Adrenocorticotropic hormone (ACTH) gel is a highly purified, sterile, long-acting formulation of the full sequence of $ACTH_{(1\text{-}39)}$ in 16% gelatin [2]. ACTH gel is indicated for 19 conditions, including infantile spasms, multiple sclerosis, and rheumatic, collagen, dermatologic, allergic, ophthalmic, respiratory and edematous diseases/disorders [2]. The dosage of ACTH gel should be individualized depending on the disease and medical condition of the patient [2]. The usual dose of ACTH gel is 40–80 units (U) given either intramuscularly or subcutaneously (sc.) every 24 to 72 h [2]. Through direct action on melanocortin receptors located in several tissue and cell types, including the bones, joints and immune system, ACTH gel is thought to have mechanisms of action that result in steroid-independent anti-inflammatory and immunomodulatory effects [3]. ACTH gel is also believed to exert steroidogenic effects by inducing cortisol from the adrenal gland [4]. While ACTH gel is indicated for use in rheumatic disorders, such as RA, limited research exists on its use in patients with refractory disease. This retrospective case series highlights the clinical features and management of five patients with refractory RA who received ACTH gel based on its proposed mechanism of action after failing several previous therapies (defined as failure to achieve disease remission with a previous treatment) (Table 1).

Case 1

A 70-year-old white male with hypertension had been treated for 10 years since the onset of RA. He had previously failed treatment with adalimumab, etanercept, abatacept, rituximab, tofacitinib and infliximab and was not a candidate for tocilizumab because of a history of diverticulitis. He presented to the clinic for a follow-up of RA reporting right wrist pain and swelling. Physical examination showed a swollen and tender right wrist but a full range of motion in all joints. The Routine Assessment of Patient Index Data with 3 measures (RAPID-3) is a patient-reported ques-

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Table 1. Patient characteristics, prior therapy and response to adrenocorticotropic hormone gel treatment.

Case	Age (years)	Previous therapy	Concomitant medications	Treatment response	Safety
1	70	Adalimumab, etanercept, abatacept, rituximab, tofacitinib, infliximab, prednisone (not a candidate for tocilizumab due to history of diverticulitis)	Methotrexate 20 mg/week, hydroxychloroquine 200 mg twice/day, folic acid 1 mg/day	Improvements in ESR, CRP, Vectra, RAPID-3 and symptoms; able to perform activities of daily living without any difficulty	Fluctuations in blood pressure throughout treatment with ACTH gel
2	75	Entanercept, adalimumab, tocilizumab, abatacept, rituximab, prednisone (discontinued methotrexate due to hair loss)	Hydroxychloroquine 200 mg twice/day	Improvements in ESR, CRP, Vectra, RAPID-3 and symptoms; able to walk 2 miles	ACTH gel was well tolerated
3	50	Adalimumab, certolizumab, abatacept, tocilizumab, prednisone	Hydroxychloroquine 200 mg twice/day	Small, temporary improvements in Vectra, RAPID-3 scores and hand pain	Erythema on upper chest, weight gain and elevated blood pressure during treatment with ACTH gel
4	62	Adalimumab, etanercept, tofacitinib (not a candidate for tocilizumab due to history of diverticulitis)	Hydroxychloroquine 200 mg twice/day, methotrexate 20 mg/week, folic acid 1 mg/day	Improvements in ESR, CRP, RAPID-3 and symptoms and joint pain; able to bend down to pick something off floor without difficulty	Increased glucose levels before and during treatment with ACTH gel
5	55	Etanercept, adalimumab, abatacept, tocilizumab, prednisone (unable to use methotrexate due to liver function test abnormalities)	None	Improvements in ESR, CRP, RAPID-3 and skin lesions; improvements in hand, hip, knee and feet swelling and pain; able to walk two miles (which she was unable to do before ACTH)	ACTH gel was well tolerated

ACTH: Adrenocorticotropic hormone; CRP: C-reactive protein.

tionnaire that provides a functional assessment, as well as classifies a patient's RA disease activity as high (>12), moderate (6.1–12), low (3.1–6) or remission (<3) [5]. At this visit, the patient's RAPID-3 score was 18.7, indicating the severity of disease as high; with pain at 9.5 and fatigue at 7 on the visual analog scales (VAS) (Table 2). The most recent Vectra DA score (2 months prior) was 75 (on a scale of 1–100), indicating high level of disease activity. Vectra DA blood test, a biomarker-based instrument, was used to measure RA disease activity and monitor therapeutic response to a treatment [6]. Erythrocyte sedimentation rate (ESR) was 65 mm/h and C-reactive protein (CRP) was 9.3 mg/l. He was prescribed ACTH gel 80 units sc. twice weekly. He remained on methotrexate and hydroxychloroquine.

After completing a full 12-week course of ACTH gel, ESR was 8 mm/h and had normalized for the first time since his diagnosis; CRP was 1.3 mg/l and was the lowest ever seen since he was diagnosed. RAPID-3 score improved to 8.5; pain and fatigue were noted at 4.5 and 2, respectively. He complained of wrist pain but no other joint pain. Since the patient positively responded to the 12-week course of ACTH gel, it was decided to continue him on maintenance therapy of ACTH gel 40 units sc. twice weekly.

During a visit 2 months later, his ESR, CRP and RAPID-3 score remained improved on maintenance therapy, and he did not have any symptomatic complaints. Since he was continuing to respond to ACTH gel, his maintenance dose was further decreased to 20 units sc. three-times weekly.

This patient had refractory RA and previously failed several medications. ACTH gel provided a reduction in inflammatory markers, as noted by ESR, CRP and Vectra results, and in reported symptoms. ACTH gel was well tolerated but his blood pressure fluctuated

throughout treatment. However, this patient was not on any medications for his hypertension.

Case 2

A 75-year-old white female with a 9-year history of RA had failed treatment with entanercept, adalimumab, tocilizumab, abatacept and rituximab, and discontinued methotrexate due to hair loss. She presented to the clinic for a follow-up of RA complaining of wrist and hand pain. Physical examination revealed bilateral wrist and knee swelling. At this visit, inflammatory markers were elevated; ESR was 84 mm/h and her CRP was 3.8 mg/l, Vectra DA score was 78 (Table 3). RAPID-3 score was 20.8, indicating high severity of RA; with pain at 7.5 and fatigue at 7 on the VAS. She was prescribed ACTH gel 80 units sc. twice weekly and remained on hydroxychloroquine.

After completing a full 12-week course of ACTH gel, she demonstrated improvements in inflammatory markers and symptoms and stated she was doing 'well.' ESR considerably dropped down to 19 mm/h and CRP to 1.5 mg/l; the last Vectra result (from a month earlier) was 50. RAPID-3 scores also improved; her score at this visit was 1.2; noting pain at 0.5 and fatigue at 1. Physical examination at this time showed only mild wrist swelling. Since the patient was responding to treatment with ACTH gel, her dose was decreased to 40 units sc. twice weekly.

The patient's ESR, CRP and RAPID-3 remained stable for 2 months after the dose reduction to 40 units twice weekly, thus the dose was then decreased to 20 units three-times weekly.

She returned a month later complaining of stiff knees and painful, swollen wrists and had an increased RAPID-3 score, although ESR and CRP continued to decrease. Since she seemed to be more symptomatic at this visit, it was decided to increase ACTH gel to 40 units twice weekly and add tofacitnib 5 mg q.d.

She returned 6 weeks later, noting improvement in knee pain and RAPID-3 score and in inflammatory markers. Since her RA was improving after the addition of tofacitnib, ACTH gel was decreased to 20 units three-times weekly again at this visit.

One month later, inflammatory markers appeared stable and she did not have any complaints. The ACTH gel dose was decreased further, to 20 units twice weekly.

One month later, inflammatory markers were the lowest they have been. At this visit, ACTH gel dose was decreased to 20 units every week.

She returned for a follow-up visit 3 months later and appeared to be doing well, with stable inflammatory markers and RAPID-3 results. It was decided to discontinue ACTH gel, while maintaining tofacitnib 5 mg twice daily.

This patient had refractory RA and previously failed several medications. ACTH gel provided a reduction in inflammatory markers, as noted by ESR, CRP and Vectra results, and in reported symptoms. For this patient, ACTH gel was used as a bridge to treatment with tofacitnib; ACTH gel was tapered down until able to be discontinued. ACTH gel was well tolerated without problems or side-effects.

Case 3

A 50-year-old white female with a 2-year history of RA had failed treatment with adalimumab, certolizumab, abatacept and tocilizumab. She presented to the clinic for a follow-up visit, post a second course of rituximab and complained of pain and swelling in the hands. Physical examination was notable for swelling and tenderness of several proximal interphalangeal (PIP) joints. A Vectra DA score of 46 indicated a high

Table 2. Overview of Case 1 test results.

Measurement	Before ACTH gel	ACTH treatment dose/measurement reading		
		ACTH gel 80 U b.i.w./ 12 weeks	ACTH gel 40 U b.i.w./ 20 weeks	ACTH gel 20 U t.i.w./ 28 weeks
ESR (mm/h)	65	8	12	11
CRP (mg/l)	9.3	1.3	1.8	3.2
Vectra	75	55[†]	54	–
RAPID-3	18.7	8.5	10.5	14.7
Pain	9.5	4.5	5	6
Fatigue	7	2	5.5	4

[†]Score from 8 weeks earlier.
ACTH: Adrenocorticotropic hormone; b.i.w.: Twice weekly; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; t.i.w.: Three-times weekly; U: Units.

Table 3. Overview of Case 2 test results.

Measurement	Before ACTH gel	ACTH treatment dose/measurement reading				
		ACTH gel 80 U b.i.w./12 weeks	ACTH gel 40 U b.i.w./20 weeks	ACTH gel 40 U b.i.w. + tofacitinib 5 mg q.d./30 weeks	ACTH gel 20 U b.i.w. + tofacitinib 5 mg q.d./38 weeks	ACTH gel 20 U q.w. + tofacitinib 5 mg q.d./50 weeks
ESR (mm/h)	84	19	30	17	8	13
CRP (mg/l)	3.8	1.5	1.7	<0.5	<0.5	<0.5
Vectra	78	50†	–	49	–	–
RAPID-3	20.8	1.2	2	2.3	1	1
Pain	7.5	0.5	0.5	0.5	0	0
Fatigue	7	1	0.5	0	0.5	0

†Score from 1 month earlier.
ACTH: Adrenocorticotropic hormone; b.i.w.: Twice weekly; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; q.d.: Every day; q.w.: Once weekly; U: Units.

level of disease activity; ESR and CRP were 4 mm/h and <0.5 mh/l, respectively (Table 4). RAPID-3 was 20.2, indicating high severity of disease; she noted pain as 8 and fatigue as 5.5 on the VAS. At this visit, she was prescribed ACTH gel 80 units sc. twice weekly and remained on hydroxychloroquine.

She returned for a follow-up after 4 weeks of ACTH gel treatment with improvements in RAPID-3 and Vectra scores. ESR and CRP levels remained the same. She stated she noticed some facial swelling and erythema over her upper chest since starting ACTH gel treatment, but continued treatment.

She returned 6 weeks later complaining of hand pain. Physical examination noted several slightly swollen and tender PIP joints. Since her last visit, she had gained 10 pounds and her blood pressure had elevated. RAPID-3 scores had increased to 17.3, as well as Vectra DA score to 49, but ESR and CRP remained stable. At this visit, she was discontinued from ACTH gel, prescribed tofacitinib 5 mg q.d. and remained on hydroxychloroquine.

This patient had refractory RA and previously failed several medications. ACTH gel provided a small and temporary improvement in Vectra and RAPID-3 scores. This patient experienced erythema on her upper chest, weight gain and elevated blood pressure while on ACTH gel. Her facial swelling and erythema resolved upon ACTH gel discontinuation.

Case 4

A 62-year-old black female with hypertension, diabetes and a 1-year history of RA had failed treatment with adalimumab, etanercept, tofacitinib and was unable to take tocilizumab due to a history of diverticulitis. She presented to the clinic for a follow-up of RA after a course of rituximab, complaining of widespread joint pain and swelling. Physical examination was notable for swollen and tender PIP joints and tenderness of the right knee. Inflammatory markers were elevated – ESR was 85 mm/h and CRP was 2.4 mg/l (Table 5). RAPID-3 score was an 8; noting pain and fatigue at 2.5 each on the VAS. Glucose levels were 196 mg/dl at this visit, down from 388 mg/dl 6 weeks previously. At this visit, she was prescribed ACTH gel 80 units sc. twice weekly and remained on hydroxychloroquine, methotrexate and folic acid.

Table 4. Overview of Case 3 test results.

Measurement	Before ACTH gel	ACTH treatment dose/measurement reading	
		ACTH gel 80 U b.i.w./4 weeks	ACTH gel 80 U b.i.w./10 weeks
ESR (mm/h)	4	4	4
CRP (mg/l)	<0.5	<0.5	<0.5
Vectra	46	42	49
RAPID-3	20.2	16.5	17.3
Pain	8	7	7
Fatigue	5.5	5.5	4

ACTH: Adrenocorticotropic hormone; b.i.w.: Twice weekly; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; U: Units.

Table 5. Overview of Case 4 test results.

Measurement	Before ACTH gel	ACTH treatment dose/measurement reading	
		ACTH gel 80 U b.i.w./6 weeks	ACTH gel 80 U b.i.w./12 weeks
ESR (mm/h)	85	76	38
CRP (mg/l)	2.4	1.8	1.3
RAPID-3	8	7.7	6.3
Pain	2.5	2.5	2
Fatigue	2.5	2.5	2

ACTH: Adrenocorticotropic hormone; b.i.w.: Twice weekly; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; U: Units.

Upon completion of a 12-week course of ACTH gel, she reported feeling 'better.' Physical examination identified her PIP joints were not swollen. Inflammatory markers had continued to decrease; ESR was 38 mm/h and CRP was 1.3 mg/l. RAPID-3 scores also decreased to 6.3; she rated pain and fatigue at 2 each on the VAS. At this visit, she had an elevated glucose level of 244 mg/dl. She positively responded to the 12-week course of ACTH gel and it was decided to discontinue ACTH gel, which had been used as bridge therapy, and start her on another course of rituximab.

This patient had refractory RA and previously failed several medications. ACTH gel provided improvements in inflammatory markers and reported symptoms. In this case, ACTH gel was used to bridge therapy with rituximab. ACTH gel was well tolerated; however, this patient experienced increased glucose levels during the course of therapy. This patient had a known diagnosis of diabetes and unstable glucose levels before treatment with ACTH gel. After ACTH gel was discontinued, her glucose levels remained unstable.

Case 5

A 55-year-old white female with diabetes and a 7-year history of RA had failed treatment with etanercept, adalimumab, abatacept, tocilizumab and was unable to use methotrexate due to liver function test abnormalities. While on tocilizumab for RA, she developed psoriatic lesions. She did not have a previous personal or family history of psoriasis and it is uncertain whether she developed drug-induced psoriasis or had psoriatic arthritis.

The patient presented to the clinic for a follow-up of her RA complaining of swelling and pain in her hands, hips, knees and feet. Physical examination noted widespread soft tissue tender points, rough skin over her elbows and cracking and erythema over the soles of her feet. Inflammatory markers were elevated; ESR was 40 mm/h and CRP was 1.8 mg/l. RAPID-3 score was 18.8 indicating high-disease severity; she noted pain and fatigue at 9 each on the VAS (Table 6). At this visit, she was prescribed ACTH gel 40 units sc. twice weekly; because of a recent diagnosis of diabetes mellitus she was not prescribed 80 units twice weekly. Her most recent glucose levels were 186 mg/dl (1 month prior to this visit) and 116 mg/dl (at this visit).

She returned to the clinic after 8 weeks of ACTH gel and stated she felt 'great'; she did not complain of pain or swelling and her skin improved. Inflammatory markers decreased; ESR was now 16 mm/h and CRP was 0.9 mg/l. RAPID-3 scores also improved to 16.7; she noted pain at 5 and fatigue at 8.5. ACTH gel 40 units sc. was continued twice weekly.

This patient had refractory RA and previously failed several medications. ACTH gel provided improvements in the patient's inflammatory markers and reported symptoms. ACTH gel was well tolerated

Table 6. Overview of Case 5 test results.

Measurement	Before ACTH gel	ACTH treatment dose/measurement reading	
		ACTH gel 40 U b.i.w./1 week	ACTH gel 40 U b.i.w./8 weeks
ESR (mm/h)	40	26	16
CRP (mg/l)	1.8	1.3	0.9
RAPID-3	18.8	15.7	16.7
Pain	9	9	5
Fatigue	9	9	8.5

ACTH: Adrenocorticotropic hormone; b.i.w.: Twice weekly; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; U: Units.

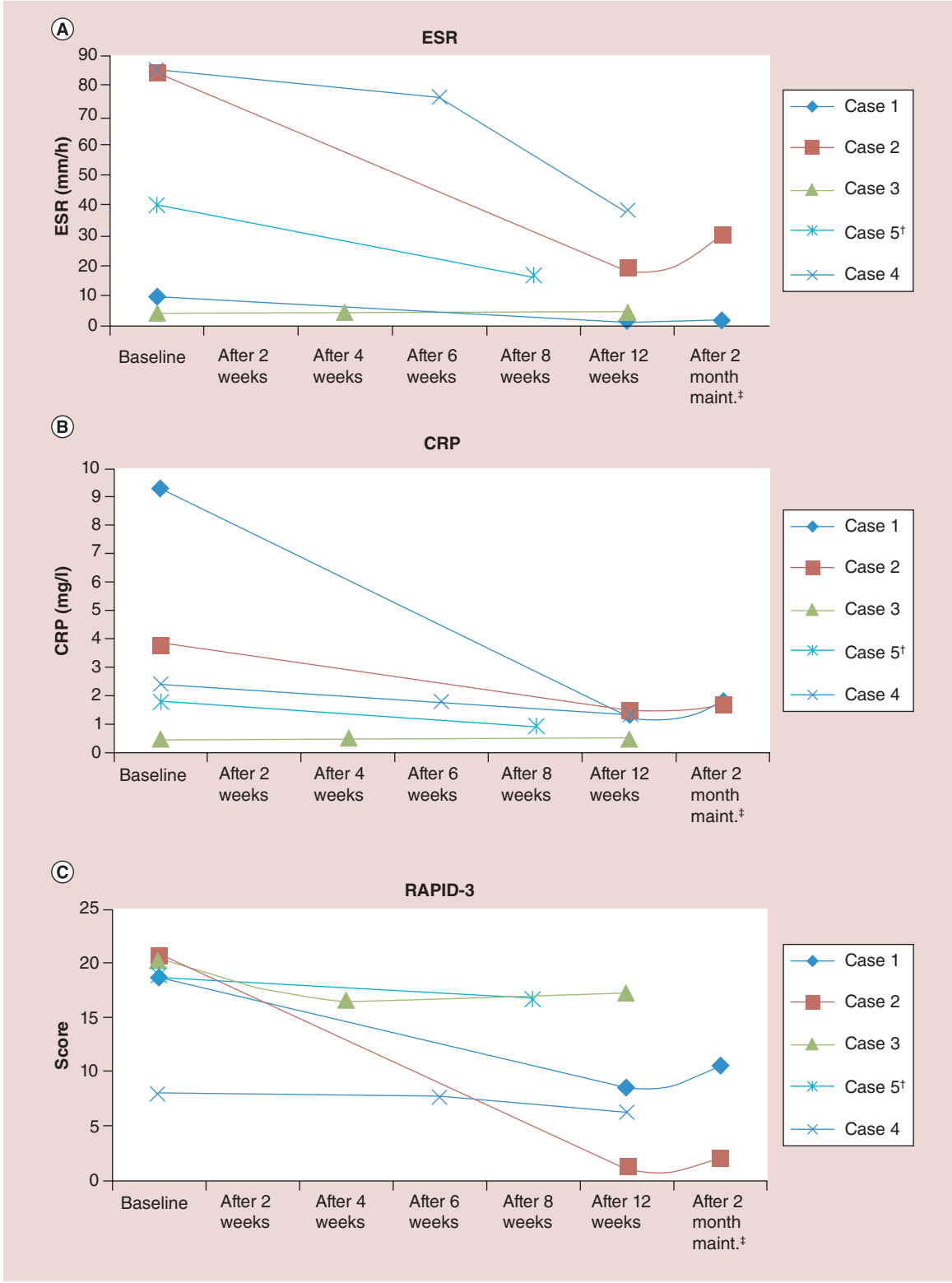

Figure 1. Erythrocyte sedimentation rate, C-reactive protein, and RAPID-3 scores on adrenocorticotropic hormone gel. (A) ESR levels on ACTH gel, **(B)** CRP levels on ACTH gel and **(C)** RAPID-3 scores on ACTH gel.
CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate.
†All Case 5 doses were 40 U BIW.
‡Maintenance dose = 40 U BIW.
maint.: Maintenance; ACTH: Adrenocorticotropic hormone.

without side-effects. Her glucose levels are continually monitored given her recent diagnosis of diabetes mellitus, but remain normal and stable.

Discussion

All patients in this case series had previously failed treatment with at least two, but up to five disease-modifying antirheumatic drugs (DMARDs), or could not use alternate DMARDs due to liver function test abnormalities, diverticulitis or other medical conditions. As this is a retrospective case series, primary or secondary end points were not established; however, ACTH gel provided an improvement in inflammatory markers and/or patient-reported symptoms in each case. Some patients experienced a small and temporary improvement in RA, while other patients experienced substantial improvements in ESR, CRP and RAPID-3 (Figure 1), and Vectra DA scores. All patients noted at least some improvement in their RA symptoms (less pain and joint swelling and tenderness) and noted they were able to perform activities of daily life with less difficulty. In some cases, ACTH gel was used to bridge patients' treatment with DMARDs, such as rituximab or tofacitinib; in another case, the ACTH gel dose was decreased and continued as maintenance treatment.

Three patients in this case series experienced fluctuations in blood pressure, weight or glucose levels. These adverse effects are known to occur with elevated cortisol and may occur with ACTH gel due to its steroidogenic effects [2]. Two of the patients in this case series tolerated ACTH gel well and without any adverse events.

Since this article is an observational case series and not a placebo-controlled, randomized, double-blind clinical trial, there are limitations, including the small sample size of patients. Nevertheless, this case series provides real-world evidence of the use of ACTH gel clinical practice for patients with refractory RA.

Conclusion

Results from this case series indicate ACTH gel may be a safe and viable option for patients with refractory RA who have failed previous therapy with multiple RA treatments. ACTH gel may provide an anti-inflammatory and immunomodulatory effects beyond steroidogenesis [3] and could be considered as a therapeutic alternative for patients with treatment-refractory RA.

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Informed consent disclosure

The author states that he has obtained verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report.

Ethical conduct of research

The author states that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Executive summary

- Preclinical evidence suggests adrenocorticotropic hormone (ACTH) gel may provide anti-inflammatory and immunomodulatory effects beyond steroidogenesis.
- ACTH gel provided an improvement in inflammatory markers and/or patient-reported symptoms in each case.
- ACTH gel was well tolerated and has an adverse event profile similar to corticosteroids; three patients experienced fluctuations in blood pressure, weight and/or glucose levels.
- ACTH gel may be a safe and viable option for patients with refractory rheumatoid arthritis who have failed previous therapy with multiple rheumatoid arthritis treatments.

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