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REVIEW ARTICLE

Acthar® Gel Treatment for Patients with Autoimmune and Inflammatory Diseases: An Historical Perspective and Characterization of Clinical Evidence

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Abstract

Acthar® Gel (repository corticotropin injection) is a naturally sourced complex mixture of adrenocorticotropic hormone analogs and other pituitary peptides that is believed to have both steroidogenic and nonsteroidogenic immunomodulatory effects via activation of melanocortin receptors in various cells throughout the body. Since 1952, Acthar has been approved by the US Food and Drug Administration to treat a variety of autoimmune and inflammatory diseases. Since 2014, Mallinckrodt Pharmaceuticals has conducted a large number of preclinical, clinical, and real-world-evidence studies of Acthar for the treatment of rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis and polymyositis, multiple sclerosis relapse, ophthalmic disorders, sarcoidosis, and nephrotic syndrome. To date, Acthar has been the subject of more than 500 publications, many of which demonstrate the safety and efficacy of Acthar in patients with inflammatory diseases for whom standard treatments were ineffective or intolerable. Here, we review the history of Acthar and the findings of studies that have investigated the mechanism of action, safety, efficacy, and real-world effectiveness of Acthar for the treatment of inflammatory diseases.

Plain Language Summary

Acthar® Gel is an anti-inflammatory drug that directly affects the immune system in a manner that differs from other anti-inflammatory drugs, such as corticosteroids. Since 1952, Acthar has been approved by the U.S. Food and Drug Administration to treat a variety of diseases involving inflammation. The commercial rights to produce Acthar have changed hands several times over the years, beginning with Armour Pharmaceuticals and most recently ending with Mallinckrodt Pharmaceuticals in 2014. Since then, Mallinckrodt has conducted multiple studies in animals to demonstrate the function of Acthar compared with other anti-inflammatory drugs. Further, several clinical trials in humans and studies of hospital or clinical practice records have confirmed the safety and effectiveness of Acthar as a treatment for many inflammatory diseases.

For a podcast discussion by the authors on Acthar® Gel see online [https://doi.org/10.1007/s40261-023-01303-5]

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Infographic

Clinical Drug Investigation

PEER-REVIEWED FEATURE

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Jeffrey Kaplan, Anca Askanase, David Chu, Abdul Abdellatif, Dhiman Basu, Mehdi Mirsaeidi

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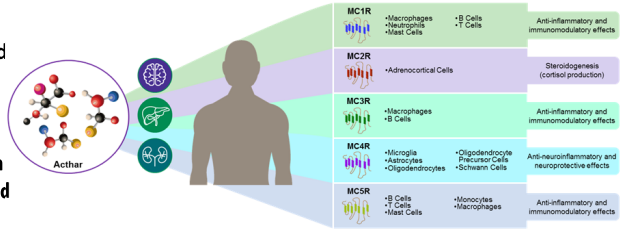
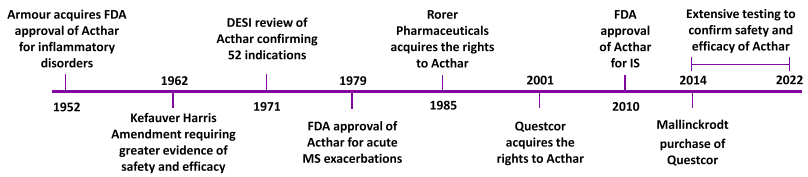
Acthar Gel is a naturally sourced complex mixture of adrenocorticotropic hormone (ACTH) analogs and other pituitary peptides derived from the entire porcine pituitary gland



Acthar has a distinct mechanism of action via activation of melanocortin receptors



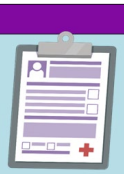
Key findings

Acthar has an extensive 70-year history of use

Since 2014, Mallinckrodt Pharmaceuticals has initiated or funded:

>20 preclinical mechanistic studies, 8 clinical studies, and >50 health economics and outcomes research and real-world evidence studies

Acthar has been the subject of >500 published manuscripts and abstracts to date



The safety and efficacy of Acthar have been investigated in clinical trials across a variety of indications

Rheumatoid Arthritis

>60% of subjects taking Acthar for 12 weeks achieved low disease activity and most maintained it 3 months following discontinuation

Dermatomyositis or Polymyositis

70% of subjects showed disease improvement with significant decreases in their corticosteroid doses after 24 weeks of Acthar treatment

Noninfectious Keratitis

Subjects displayed improvements in assessments for dry eye, visual discomfort, and pain following 12 weeks of Acthar treatment

Pulmonary Sarcoidosis

Subjects taking Acthar showed improvement in their pulmonary function tests and patient-reported outcomes including fatigue

Multiple Sclerosis

Subjects taking Acthar showed greater improvement in disease assessment scores vs placebo as early as day 7

Systemic Lupus Erythematosus

Subjects displayed significant improvements in disease activity scores after 4 weeks or 6 months of Acthar treatment

Overall

Side effects of Acthar were mostly mild or moderate with no new or unexpected safety concerns observed in these trials

Results from recent clinical studies demonstrate the safety and efficacy of Acthar in patients with inflammatory diseases for whom standard treatments have become ineffective or are associated with intolerable side effects

Abbreviations:
ACTH, adrenocorticotropic hormone; DESI, Drug Efficacy Study Implementation; FDA, US Food and Drug Administration; IF, infantile spasms; MS, multiple sclerosis.

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Key Points

Acthar® Gel is an anti-inflammatory drug that directly affects the immune system in a manner that differs from other anti-inflammatory drugs, such as corticosteroids.

Since 1952, Acthar has been approved by the US Food and Drug Administration to treat a variety of diseases involving inflammation; since 2014, Mallinckrodt Pharmaceuticals has conducted multiple studies in animals to demonstrate the function of Acthar compared with other anti-inflammatory drugs.

Furthermore, several clinical trials in humans and studies of hospital or clinical practice records have confirmed the safety and effectiveness of Acthar as a treatment for many inflammatory diseases.

1 Introduction

Acthar® Gel (repository corticotropin injection) is a naturally sourced complex mixture of adrenocorticotropic hormone (ACTH) analogs and other pituitary peptides [1], derived from the entire porcine pituitary gland. The Acthar mixture is solubilized in a 16% gelatin formulation designed for prolonged release after subcutaneous or intramuscular injection [2, 3]. A major active component is N-25 deamidated, full-length porcine $ACTH_{1–39}$ [3]. ACTH is cleaved from its pro-opiomelanocortin prohormone, as are other melanocortin signaling peptides, including α-melanocyte-stimulating hormone (α-MSH), β-MSH, and γ-MSH, all of which have been shown to have anti-inflammatory effects [4–9].

Acthar is believed to have anti-inflammatory and immunomodulatory effects by activating melanocortin receptors (MCRs) in various cell types throughout the body [10]. Although Acthar can stimulate the adrenal cortex to induce steroidogenesis, studies in healthy human subjects have demonstrated substantially lower cortisol production with Acthar compared with synthetic $ACTH_{1–24}$ depot, at amounts slightly above normal endogenous levels [3, 11]. An 80 U subcutaneous dose of Acthar produced mean peak total cortisol (E_{max}) levels of 22.2 µg/dL at 24 h [11].

Analysis of Acthar binding and activation of all 5 MCRs demonstrated a distinct activity profile compared with synthetic MCR agonists [12]. Acthar's lowest full agonistic activity is at MC2R, which is expressed in adrenocortical cells to promote steroidogenesis, whereas synthetic $ACTH_{1–24}$ has its highest activity at MC2R. This was consistent with substantially less endogenous corticosteroid production in rats and humans exposed to Acthar compared with synthetic $ACTH_{1–24}$ [11, 12]. The relatively low endogenous cortisol production by Acthar eliminates the need for cortisol level testing or hypersensitivity skin tests during clinical use [3, 11, 12].

Acthar has been shown to exert a direct immunomodulatory effect on B cells and macrophages, independent from its steroidogenic activity [13, 14]. The expression of genes involved in B-cell proliferation and function were downregulated in response to Acthar [15]. This effect was not recapitulated by individual pituitary neuropeptides, including $ACTH_{1–39}$, $ACTH_{1–24}$, and α-MSH [15]. In addition, Acthar was shown to inhibit B-cell activation and antibody production via suppression of toll-like receptor (TLR) 9 and B-cell receptor engagement [16]. Inflammatory cytokine production from human macrophages was reduced in vitro by Acthar in a steroid-independent manner [14]. Moreover, in a mouse model of relapsing-remitting multiple sclerosis (MS), Acthar inhibited inflammation and demyelination within the spinal cord and suppressed ex vivo myelin peptide-induced $CD4^+$ T-cell proliferation [17]. Taken together, these studies confirm a different mechanism of action for

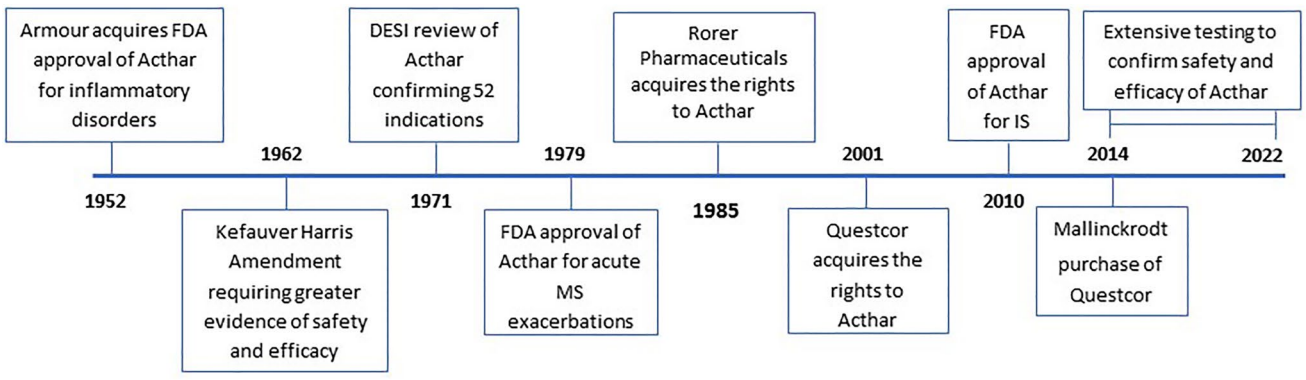

Fig. 1 Timeline of key events regarding Acthar. *DESI* Drug Efficacy Study Implementation, *FDA* US Food and Drug Administration, *IS* infantile spasms, *MS* multiple sclerosis

Acthar compared with other anti-inflammatory drugs (electronic supplementary material [ESM] Fig. S1).

2 History of Acthar

Acthar was initially developed by Armour Pharmaceuticals and was approved by the US Food and Drug Administration (FDA) in 1952 for many indications [18], including connective tissue diseases (e.g., systemic lupus erythematosus [SLE], psoriatic arthritis, and rheumatoid arthritis [RA]), hypersensitivities (contact dermatitis, severe asthma, and hay fever), acute inflammatory disorders of the eye or skin, proteinuria in nephrotic syndrome, and many other inflammatory diseases. The initial approval was prior to the Kefauver Harris Amendment of 1962 that required drug manufacturers to provide evidence of efficacy prior to FDA approval [2, 19]. A Drug Efficacy Study Implementation review conducted between 1971 and 1977 concluded that Acthar was effective for 52 indications, and the label was expanded accordingly. Following the Drug Efficacy Study Implementation review, the approved indications included numerous disorders such as endocrine, opthalmic, respiratory, and dermatologic diseases, as well as allergic conditions.

In 1979, Acthar was approved by the FDA for the treatment of MS exacerbations in adults [18]. Due to development of corticosteroid therapies, Acthar fell out of favor in the 1980s for some conditions and was largely replaced by prednisone for many indications [20]. In 1985, Rorer Pharmaceuticals acquired the rights to Acthar, and the company later merged with Rhone-Poulenc to form Rhone-Poulenc Rorer. There was a shortage of Acthar in the mid-1990s, as Rhone-Poulenc Rorer had chosen to discontinue the product. However, in response to requests from physicians and patient groups, a limited amount of Acthar was produced, although demand still far exceeded the supply [20]. The complex and expensive purification process became unsustainable, and Aventis (which was formed in 1999 from a merger of Rhone-Poulenc Rorer and Hoechst) sold the rights to Acthar to Questcor Pharmaceuticals in 2001 [20].

Multiple research studies were initiated and published by Questcor, which helped characterize Acthar's mechanism of action [21–24]. One such study provided evidence of Acthar's immunomodulatory activity and related efficacy in a mouse model of SLE [24]. In a transgenic mouse model of amyotrophic lateral sclerosis, Acthar was found to delay symptoms of disease onset and reduce the levels of toxic superoxide dismutase both in the mouse and in cultured fibroblasts [22]. Arnason et al. described the corticosteroid-independent effects of Acthar and other melanocortins relevant for clinical management of MS [21]. Similarly, Berkovich et al. presented a review to further characterize the complex and dynamic mechanism of action of Acthar via the MCR system in MS exacerbations [23].

For many years, Acthar was used as first-line therapy for infantile spasms, even though it was not an FDA-approved indication. Baram et al. demonstrated that a 2-week course of Acthar (150 U/m^2/day) was more effective than prednisone (2 mg/kg/day) in the suppression of spasms and hypsarrhythmia [1, 25]. A positive response was reported in 86.6% of patients who achieved cessation of spasms and elimination of hypsarrhythmia with no discontinuation or modification of the therapy [25]. In 2004, the American Academy of Neurology and the Child Neurology Society reported that ACTH is likely effective for the short-term treatment of infantile spasms and resolution of hypsarrhythmia, although there was insufficient evidence to recommend an optimal dosage or duration of treatment [26]. Questcor invested in research and development to attain FDA approval of Acthar for the management of infantile spasms in 2010 [20]. In addition, Questcor agreed to remove 33 of the previously approved indications to conform with modern labeling requirements, leaving a total of 19 indications (ESM Table S1) [1, 27]. An updated 2012 report by the American Academy of Neurology and the Child Neurology Society reinforced the use of Acthar in treating infantile spasms [28].

Mallinckrodt Pharmaceuticals purchased Questcor in 2014, focused on modernizing the manufacturing of Acthar, and initiated research activities to further evaluate the safety and efficacy of the drug (Fig. 1) [29]. Substantial data about Acthar have been generated from at least 20 preclinical mechanistic studies, more than 50 real-world evidence/health economics and outcomes research studies, and 8 clinical studies targeting approximately 900 enrolled patients [29]. To date, more than 500 manuscripts and abstracts have been published regarding Acthar [29].

In 2021, the Acthar label was changed to provide up-to-date safety information and remove the statement: "common adverse reactions for Acthar Gel are similar to those of corticosteroids" on the basis of extensive pharmacovigilance and clinical trial data [30, 31]. Based on analysis of decades of pharmacovigilance data, the most commonly reported adverse effects related to Acthar use include injection site reaction, fatigue, fluid retention, insomnia, headache, high blood glucose levels, hypertension, increased risk of infections, and irritability [1, 30].

3 Clinical Studies of Acthar: 2014–2022

3.1 Rheumatoid Arthritis

The use of Acthar for the treatment of RA was assessed in a randomized, placebo-controlled withdrawal trial [32]. No

Table 1 Clinical and real-world evidence studies of Acthar in rheumatoid arthritis

References	Study type	Patients enrolled	Acthar dosing	Key efficacy outcomes	Common AEs in the Acthar group (≥ 3% frequency)	Serious AEs
Fleischmann et al., 2020 [32]	RCT	259	80 U twice weekly for 12 weeks (part 1, open-label period); 80 U or placebo twice weekly for 12 weeks (part 2, double-blind period)	At week 12, 163 (62.9%) patients achieved LDA with Acthar; at week 24, 47 (61.0%) Acthar-treated subjects vs. 32 (42.1%) placebo-treated subjects maintained LDA ($p=0.019$)	Headache ($n=9$ in the open-label period; $n=5$ in the double-blind period), urinary tract infection ($n=10$ in the open-label period), hyperglycemia ($n=3$ in the double-blind period), and hypertension ($n=3$ in the double-blind period)	Pneumonia[a], chest pain, and craniocerebral injury (1 case each)
Fleischmann et al., 2022 [33]	Post hoc analysis of RCT	258	80 U twice weekly for 12 weeks	PROs for pain, disability, fatigue, activity impairment, and work impairment showed greater improvement in patients who were Acthar responders (DAS28-ESR scores <3.2)	NA	NA
Fleischmann et al., 2022 [34]	Post hoc analysis of RCT	258	80 U twice weekly for 12 weeks	Predictors of response to Acthar included lower baseline TJC ($p=0.0310$), SJC ($p=0.0018$), ESR ($p=0.0487$), and CDAI ($p=0.0112$) and shorter RA duration ($p=0.0446$); negative predictors of response were OA ($p=0.0272$) and other joint-related conditions ($p=0.0193$)	NA	NA

Table 1 (continued)

References	Study type	Patients enrolled	Acthar dosing	Key efficacy outcomes	Common AEs in the Acthar group (≥ 3% frequency)	Serious AEs
Hayes et al., 2021 [35]	Cohort claims database analysis	350 (Acthar); 162,065 (control)	Not reported	Indicators of Acthar initiation included higher Charlson comorbidity index scores ($p < 0.001$); RA severity index ($p < 0.001$); greater frequency of comorbidities; higher use of nontraditional DMARDs (14% vs. 2%), glucocorticoids (90% vs. 68%), and opioids (66% vs 45%); higher HCRU (all comparisons, $p < 0.001$); higher medical and total costs (both comparisons, $p < 0.0001$)	NA	NA
Hayes et al., 2021 [36]	Medical records review	114	Not reported	CDAI (-9.7 ± 16.9, $p = 0.0101$), SJC (-1.1 ± 2.8, $p = 0.0116$), TJC (-3.3 ± 8.0, $p = 0.0128$), RAPID3 (-1.1 ± 1.9, $p = 0.0036$), PGA (-1.3 ± 2.4, $p = 0.0214$), and patient assessment of pain severity scores (-1.1 ± 2.8, $p = 0.0056$) were significantly reduced 1 year post-initiation of Acthar when compared with baseline; use of conventional synthetic or biological DMARDs (-9.6%, $p < 0.05$; and -14%, $p < 0.05$, respectively), NSAIDs (-12.3%, $p < 0.05$), and opioids (-14%, $p < 0.05$) decreased 1 year post-initiation of Acthar	NA	NA

Table 1 (continued)

References	Study type	Patients enrolled	Acthar dosing	Key efficacy outcomes	Common AEs in the Acthar group (≥ 3% frequency)	Serious AEs
Busch et al., 2022 [37]	Medical records review	63	Individualized; 80 U twice weekly for most (74.6%) patients; mean duration 10.3 months	Reduced CDAI (−6.6 ± 11.3), RAPID3 (−1.2 ± 4.4), PGA (−0.7 ± 1.8), TJC (−4.1 ± 7.1), SJC (−1.3 ± 5.5), and pain VAS (−0.5 ± 1.4) when comparing ± 7 days from Acthar initiation vs. 12 months post-Acthar initiation; glucocorticoids (67% vs. 60%), opioids (41% vs. 29%), and NSAIDs (27% vs. 19%) when comparing within 12 months pre-Acthar vs. 12 months post-Acthar initiation	NA	NA

AEs adverse events, *CDAI* Clinical Disease Activity Index, *DAS28-ESR* Disease Activity Score with 28-joint count and erythrocyte sedimentation rate, *DMARDs* disease-modifying antirheumatic drugs, *ESR* erythrocyte sedimentation rate, *HCRU* health care resource utilization, *LDA* low disease activity, *NA* not applicable, *NSAIDs* nonsteroidal anti-inflammatory drugs, *OA* osteoarthritis, *PGA* Physician's Global Assessment, *PROs* patient-reported outcomes, *RA* rheumatoid arthritis, *RAPID3* Routine Assessment of Patient Index Data 3, *RCT* randomized controlled trial, *SJC* swollen joint count, *TJC* tender joint count, *VAS* visual analog scale

[a]Described as treatment-related or study drug-related

Table 2 Clinical studies of Acthar in systemic lupus erythematosus

Reference	Study type	Patients enrolled	Acthar dosing	Key efficacy outcomes	Common AEs in the Acthar group (≥3% frequency)	Serious AEs
Fiechtner and Montroy, 2014 [38]	Open-label pilot study	10	80 U for 7–15 days	Improvement in SLEDAI-2K was achieved at each weekly assessment through 28 days ($p<0.05$)	Sinus infection ($n=1$) and bilateral edema in legs/ankles ($n=1$) both resolved	None reported
Fiechtner and Montroy, 2016 [39]	6-month extension of open-label pilot study	5	80 U twice weekly	Significant improvement in SLEDAI-2K from day 0 to month 3 ($p=0.040$) and month 6 ($p=0.0007$)	Hematuria ($n=2$) at trial onset (resolved by next evaluation)	None reported
Furie et al., 2016 [40]	Phase IV pilot RCT	38	40 U daily or 80 U every other day for 8 weeks of double-blind study; open-label extension was 44 weeks	No significant difference between Acthar and placebo for the primary endpoint (composite responder index at 4 weeks); secondary measures (total hSLEDAI [$p=0.008$], total BILAG [$p=0.001$], Cutaneous Lupus Erythematosus Disease Area [$p=0.047$], and Severity Index Activity scores [$p<0.05$])were significantly improved by 8 weeks in the combined Acthar-treated groups compared with placebo	AEs occurring in the combined Acthar group included weight gain ($n=5$), abdominal pain ($n=2$), back pain ($n=2$), diarrhea ($n=2$), fatigue ($n=2$), fluid retention ($n=2$), mood changes ($n=2$), irritability ($n=2$), and oropharyngeal pain ($n=2$)	1 patient in the 40 U group experienced chest discomfort[a] and GERD[a]; 1 patient in the 80 U group experienced both hemorrhagic ovarian cyst and viral infection; 1 patient in the 80 U group died of *Klebsiella* infection
Furie et al., 2017 [41]	Post hoc analysis of RCT	38	16, 40, or 80 U 1–3 times per week through week 52 (including 44 weeks OLE)	At week 52, response rate to revised novel index (SLE responder index [SRI]) was 48% for the Acthar/Acthar group and 54.5% in the placebo/Acthar group	Pelvic infection and lower abdominal pain	Pelvic abscess ($n=1$)[a], GERD and chest discomfort ($n=1$)[a], hemorrhagic ovarian cyst and viral infection in the double-blind phase and pelvic infection and lower abdominal pain in the open-label extension ($n=1$)[a], pyelonephritis ($n=1$)[a], viral infection ($n=1$), non-cardiac chest pain ($n=1$), SLE flare with hospitalization ($n=1$), and ulcerative keratitis ($n=1$)

Table 2 (continued)

Reference	Study type	Patients enrolled	Acthar dosing	Key efficacy outcomes	Common AEs in the Acthar group (≥3% frequency)	Serious AEs
Askanase et al., 2020 [42]	Phase IV RCT	169	80 U every other day to week 4, then twice weekly to 24 weeks	No significant difference between Acthar and placebo in the proportion of SRI-4 responders; reductions from baseline to week 16 were observed for SJC/TJC (range 0–28; -6.4 ± 5.7, $p < 0.0203$), and CLASI-activity score (-4.5 ± 5.4, $p = 0.0423$) in the Acthar-treated group	Upper respiratory tract infection ($n = 9$), insomnia ($n = 7$), headache ($n = 6$), hypertension ($n = 6$), urinary tract infection ($n = 6$), influenza ($n = 4$), nasopharyngitis ($n = 3$), injection site urticaria ($n = 3$), bronchitis ($n = 3$), and hyperglycemia ($n = 3$)	Herpes zoster ($n = 1$), SLE flare ($n = 2$), and nephrotic syndrome ($n = 1$)
Askanase et al., 2021 [43]	Post hoc PRO analysis of phase IV RCT	169	80 U every other day to week 4, then twice weekly to 24 weeks	Greater improvements from baseline in several SLE QoL domains (pain, planning, fatigue) compared with placebo among patients with higher baseline SLEDAI-2K, CLASI-Activity, and BILAG-2004 scores; Acthar was associated with greater improvement of WPAI domains of percentage work missed (Acthar mean change, −8.4 [SD 25.1]; placebo mean change, 7.8 [SD 21.9]; $p = 0.0182$ for least squares mean difference), and percentage impairment while working (nominal $p < 0.01$ at week 16 in BICLA responders compared with placebo)	NA	NA

Table 2 (continued)

Reference	Study type	Patients enrolled	Acthar dosing	Key efficacy outcomes	Common AEs in the Acthar group (≥ 3% frequency)	Serious AEs
Askanase et al., 2021 [44]	Post hoc biomarker analysis of a phase IV RCT	169	80 U every other day to week 4, then twice weekly to 24 weeks	Patients receiving Acthar showed reduced levels of B cell-activating factor and interleukin-6 *vs.* placebo; lower total B cells and atypical activated memory B cells in patient subgroups with higher baseline disease activity scores and BICLA non-responders; increases in C3 and C4 vs. placebo in several subgroups	NA	NA

AEs adverse events, *BICLA* BILAG-based Combined Lupus Assessment, *BILAG* British Isles Lupus Assessment Group, *C3, C4* complement proteins 3 and 4, *CLASI* Cutaneous Lupus Erythematosus Disease Area and Severity Index, *GERD* gastroesophageal reflux disease, *hSLEDAI* hybrid Systemic Lupus Erythematosus Disease Activity Index, *NA* not applicable, *OLE* open-label extension, *PRO* patient-reported outcome, *QoL* quality of life, *RCT* randomized controlled trial, *SD* standard deviation, *SJC* swollen joint count, *SLE* systemic lupus erythematosus, *SLEDAI-2K* Systemic Lupus Erythematosus Disease Activity Index-2000, *SRI-4* Systemic Lupus Erythematosus Responder Index, *TJC* total joint count, *WPAI-Lupus* Work Production and Activity Impairment-Lupus

[a]Described as treatment-related or study drug-related

new or unexpected safety signals were observed, and more than 60% of patients achieved low disease activity by week 12 of therapy [32]. Most patients maintained low disease activity during 12 additional weeks of Acthar therapy and for 3 months following discontinuation of the drug. Correlations between patient-reported outcomes and clinical response to Acthar were investigated using data from the clinical trial [33]. Clinical responses, including Disease Activity Score with 28-Joint Count and erythrocyte sedimentation rate, total joint count, and Clinical Disease Activity Index, were found to directly correlate with patient-reported outcomes [33]. Predictors of positive response to Acthar in patients with RA included lower baseline levels for swollen joint count, total joint count, Erythrocyte Sedimentation Rate, and Clinical Disease Activity Index, as well as shorter RA duration [34]. Osteoarthritis and other joint-related conditions were predictive of negative response to Acthar [34].

A claims database analysis indicated that Acthar was initiated in patients with RA who had more severe disease, comorbidities, and concomitant use of treatments including disease-modifying antirheumatic drugs (DMARDs), corticosteroids, opioids, and nonsteroidal anti-inflammatory drugs [35]. Real-world treatment patterns for patients with RA evaluated from medical records revealed that Acthar improved clinical outcomes and lowered the need for concomitant therapies up to 1 year after initiation of treatment [36, 37]. Busch et al. reported improvements in multiple RA disease assessments 12 months after Acthar initiation, as well as reductions in opioid, glucocorticoid, and nonsteroidal anti-inflammatory drug use; a small proportion (4.3%) of patients discontinued Acthar due to adverse effects (Table 1) [37].

In an analysis of safety data from a randomized clinical trial of Acthar used as an adjunctive therapy for RA (along with DMARDs and glucocorticoids), adverse events (AEs) in the Acthar cohort were compared with those reported in 4 other randomized trials using low-dose glucocorticoids/DMARDs (without Acthar) [31]. Ten of the 16 most frequent AEs (in ≥ 1% of patients) associated with glucocorticoids/DMARD treatment occurred at a lower rate in patients treated with Acthar. These included RA flare, arthralgia, abdominal pain/gastrointestinal symptoms, nasopharyngitis, insomnia, flushing, bronchitis, chest pain, depression, and vertigo. It was concluded that there was no additional risk with the use of Acthar as an add-on therapy to low-dose glucocorticoids and DMARDs for the management of RA [31].

3.2 Systemic Lupus Erythematosus

A single-site, 4-week, open-label trial using Acthar for the treatment of moderate to severe SLE noted significant

improvements in SLE Disease Activity Index-2000 scores in patients with refractory disease [38]. No treatment-related serious or unexpected AEs were reported. A 6-month extension of the trial found significant improvements in SLE Disease Activity Index-2000 scores and decreased swollen, tender, and total joint counts through 6 months following initiation of Acthar [39].

A phase IV pilot study of Acthar for the treatment of persistent SLE noted a trend of better response in the Acthar group versus the placebo group after 8 weeks of treatment, as well as statistically significant improvement for several secondary endpoints [40]. The incidence of AEs was similar between cohorts, and Acthar was well tolerated. A post hoc analysis demonstrated durable efficacy over 52 total weeks of Acthar treatment, including an open-label extension of the pilot study. No new safety signals were identified during the 44 weeks of open-label extension [41].

In a phase IV, placebo-controlled, randomized clinical trial, the proportion of Acthar responders as assessed by the SLE Responder Index 4 did not achieve statistical significance between Acthar and placebo [42]. However, the SLE Responder Index 4 may not have been sufficiently sensitive to detect partial improvement and may only distinguish complete resolution of a symptom. Acthar treatment did show disease improvement in several secondary efficacy assessments. No new safety signals or unexpected AEs were reported. Patient-reported outcomes indicated that Acthar provided improvements in quality of life and work productivity versus placebo over the 24-week trial [43]. Biomarker analysis revealed that Acthar reduced inflammation through B-cell immunomodulation (Table 2) [44].

A narrative review found that pooled data from 3 clinical trials of SLE showed significant improvement of British Isles Lupus Assessment Group 2004 index scores after 8 weeks of Acthar therapy, and decreased tender and swollen joint counts after 4 weeks. Few serious AEs were reported in the trials and Acthar exhibited an acceptable safety profile [45].

3.3 Dermatomyositis and Polymyositis

An observational registry study of dermatomyositis and polymyositis found that Acthar therapy resulted in an

Table 3 Clinical and real-world evidence studies of Acthar in dermatomyositis and polymyositis

References	Study type	Patients enrolled	Acthar dosing	Key efficacy outcomes	Common AEs in the Acthar group (≥ 3% frequency)	Serious AEs
Levine et al., 2016 [46]	Registry analysis	24	80 U twice weekly; mean duration 6 months	14/24 patients responded to Acthar	Worsening diabetes ($n=3$), edema ($n=1$), lower extremity edema ($n=2$), gastric reflux ($n=1$), headache ($n=1$), hypertension ($n=1$), nausea ($n=1$), vertigo ($n=1$), and weight gain ($n=1$)	None reported
Aggarwal et al., 2018 [48]	Prospective proof-of-concept study	11	80 U SC twice weekly for 24 weeks	7/10 patients met the primary endpoint of International Myositis Assessment and Clinical Studies criteria for improvement at a median of 8 weeks	Injection site rash or bruising ($n=4$)[a], diarrhea ($n=1$)[a], anxiety ($n=1$)[a], insomnia ($n=2$)[a], calcinosis ($n=2$)[a], depression ($n=1$)[a], agitation ($n=1$)[a], herpes pneumonitis ($n=1$)[a], tachycardia ($n=1$)[a], high cholesterol ($n=1$)[a], hyperglycemia ($n=3$)[a], sinusitis and upper respiratory infection ($n=2$)[a], and hypertension ($n=2$)[a]	Herpes zoster ($n=1$)[a], disseminated herpes zoster ($n=1$)[a], avascular necrosis ($n=1$)[a], chest pain ($n=1$)[a], and AV heart block ($n=1$)

AEs adverse events, *AV* atrioventricular, *SC* subcutaneously

[a]Described as treatment-related or study drug-related

improved clinical course in 14/24 patients, suggesting that it is an effective option for refractory dermatomyositis/polymyositis. Mild to moderate AEs were reported in 10 patients, including worsening diabetes in some patients [46].

Seven of 9 patients who completed 24 weeks of Acthar treatment in an open-label study of refractory dermatomyositis showed improvements in Cutaneous Dermatomyositis Disease Area and Severity Index and Physician's Global Assessment scores [47]. AEs were mild and no patients stopped medication during the study [47]. Another study also noted improvement of refractory dermatomyositis/polymyositis in 70% of patients during 24 weeks of Acthar therapy, with a significant decrease in steroid dose [48]. Four serious treatment-related AEs occurred (2 of which were due to herpes zoster), but overall, Acthar was considered to be well tolerated [48].

A real-world profile of Acthar usage patterns and outcomes showed improvement of dermatomyositis/polymyositis in 66.7% of patients, based on a medical records review. In this observational study, 25% of patients with dermatomyositis/polymyositis had treatment-related AEs that required discontinuation (Table 3) [49].

3.4 Multiple Sclerosis Relapse

Results of an observational prospective registry study of MS relapse found that patients treated with Acthar showed significant improvements in disease assessment scores, including the MS Impact Scale Version 1, the Clinical Global Impression of Improvement, and Work Productivity and Activity Impairment Questionnaire: MS at 2- and 6-month timepoints [50]. A follow-up analysis of the registry study showed that American Academy of Neurology quality metrics guidelines were followed by health care professionals during Acthar treatment in patients with MS relapse, and Acthar was associated with improved outcomes in the domains of disability, fatigue, cognitive impairment, depression, and quality of life [51].

A randomized controlled trial for treatment of MS relapse that inadequately responded to corticosteroids showed greater response/improvement for patients who received Acthar versus placebo at days 7, 21, and 42 on the Expanded Disability Status Scale and Clinical Global Impression of Improvement. No serious AEs or deaths were reported. It was concluded that Acthar was effective for patients with MS that was not responsive to corticosteroid treatment (Table 4) [52].

3.5 Ocular Cicatricial Pemphigoid

A case study of a patient with ocular cicatricial pemphigoid who was treated for 19 months with Acthar demonstrated significant improvement of ocular surface inflammation in conjunction with tapering of systemic steroid use. No serious AEs were observed (Table 5) [53].

3.6 Optic Neuritis

In an open-label, single-arm study of acute demyelinating optic neuritis, patients who began Acthar therapy within 2 weeks of symptom onset and were treated for 15 days showed improvements in visual acuity tests over the course of 400 days following onset of disease [54]. Visual acuity improvements were noted for the eye affected with optic neuritis, as well as the contralateral eye, and it was concluded that further studies exploring the potential efficacy of Acthar were warranted. Two serious treatment-related AEs were reported, including an allergic reaction and an MS relapse (Table 5) [54].

3.7 Uveitis

A medical records review of uveitis noted that 84% of patients who had begun Acthar therapy within the previous 12 months had improvement of vision. Concomitant medications were reduced during Acthar therapy and no patients had worsening disease (Table 5) [55].

3.8 Retinal Vasculitis

In a prospective, open-label, single-arm study, patients with noninfectious vasculitis showed improvement in retinal vasculitis severity scoring in 16 of 30 eyes following 12 weeks of Acthar therapy. One patient discontinued treatment due to an injection site reaction, but Acthar was well tolerated overall and considered a potentially effective therapy (Table 5) [56].

3.9 Noninfectious Keratitis

A phase IV open-label study of noninfectious keratitis showed disease improvements following 12 weeks of Acthar treatment, as determined by assessments for dry eye, ocular discomfort, and pain [57]. Acthar was determined to be effective, with no new safety signals identified. Similarly, a pilot study of Acthar for dry eye disease found significant improvements via assessments of erythema and superficial punctate keratitis lesions using either corneal fluorescein or lissamine green staining. Symptom Assessment in Dry Eye scores also showed improvement with Acthar. No ocular AEs were observed and intraocular pressure significantly decreased by day 84 of Acthar treatment (Table 5) [58].

Table 4 Clinical and real-world evidence studies of Acthar in multiple sclerosis relapse

Reference	Study type	Patients enrolled	Acthar dosing	Key efficacy outcomes	Common AEs in the Acthar group (≥3% frequency)	Serious AEs
Kaplan et al., 2020 [50]	Prospective, observational registry study	145	Individualized/variable	Mean MSIS-29v1 physical subscale scores improved at 2 months (−8.0; $p=0.0002$) and 6 months (−9.6; $p<0.0001$)	MS relapse ($n=5$) and urinary tract infection ($n=4$)	MS relapse ($n=5$), urinary tract infection ($n=2$), asthenia ($n=2$), cellulitis ($n=1$), concussion ($n=1$), intentional overdose ($n=1$), atrial fibrillation ($n=1$), dehydration ($n=1$), and dyspnea ($n=1$)
Kaplan et al., 2021 [51]	Retrospective analysis of data from registry study	125	Individualized/variable	AAN metrics including activity impairment (− 11.5; $p=0.0003$ at month 6), work time missed (−27.8; $p=0.0255$), fatigue (−6.7; $p=0.02$ at 2 months), cognitive impairment (−5.2; $p=0.01$ at 2 months), clinical depression (−6.3; $p=0.03$ at 6 months), and MSIS-29 psychological subscale (QoL measure; − 7.9; $p=0.0040$ at month 2; − 9.9; $p=0.0012$ at month 6) improved with Acthar therapy compared with baseline; AAN guidelines for MS relapse were followed	NA	NA
Wynn et al., 2022 [52]	RCT	35	80 U daily for 14 days	61.1% (90% CI 42.0–77.3) EDSS responders in the Acthar group; 11.8% (90% CI 4.0–30.1) responders in placebo subjects	Injection site bruising ($n=3$), injection site erythema ($n=1$), contusion ($n=2$), arthralgia ($n=1$), and insomnia ($n=2$)	None reported

AAN American Academy of Neurology, *AEs* adverse events, *CI* confidence interval, *EDSS* Expanded Disability Status Scale, *MS* multiple sclerosis, *MSIS-29v1* Multiple Sclerosis Impact Scale version 1, *NA* not applicable, *QoL* quality of life, *RCT* randomized controlled trial

Table 5 Clinical and real-world evidence studies of Acthar in ophthalmic diseases

References	Study type	Patients enrolled	Acthar dosing	Key efficacy outcomes	Common AEs in the Acthar group (≥ 3% frequency)	Serious AEs
Sharon et al., 2018 [53]	Case study of ocular cicatricial pemphigoid	1	80 U twice weekly for 19 months	Significant improvement of ocular surface inflammation; stabilized visual acuity	Not reported	None observed
Scannell Bryan et al., 2019 [54]	Open label, single-arm study of acute demyelinating optic neuritis	25	80 U daily for 5 days followed by 40 U for 10 days	High-contrast visual acuity improved in the affected eye through 400 days from disease onset (52.5 ± 3.1 vs. 36.2 ± 2.4 letters correct); low-contrast acuity improved in both affected (6.8 ± 1.3 vs. 1.8 ± 1.0 letters correct) and contralateral eyes (11.7 ± 1.3 vs. 8.3 ± 1.0 letters correct) compared with baseline	Posterior vitreous detachment; spots in vision, change in hearing, nausea; and hand numbness ($n = 3$ for each)	Allergic reaction[a], MS relapse, and breast cancer diagnosis ($n = 3$ for each)
Nelson et al., 2019 [55]	Medical records review of uveitis	91	40–80 U once or twice weekly; duration individualized	76 (84%) patients improved after Acthar treatment, and none worsened; vision improvement was observed in 86% of patients	NA	NA
Anesi et al., 2021 [56]	Proof-of-concept study of retinal vasculitis	30 total eyes	80 U twice weekly for up to 24 weeks	Improvements in 16 and 15 eyes by RVSS and RL, respectively; complete resolution of disease by RL was reported in 7 eyes within a mean time of 17.1 weeks	Injection site reaction ($n = 1$)[a], insomnia ($n = 2$)[a], mood change ($n = 1$)[a], dizziness and nausea ($n = 1$)[a], loss of appetite ($n = 1$)[a], and inflammation ($n = 4$)	None reported
Wirta et al., 2021 [57]	Phase IV open-label study of keratitis	35	80 U twice weekly for 12 weeks	≥ 12-point improvement in IDEEL symptom bother domain observed in 17 (50%) patients; 15 (44.1%) and 5 (14.7%) achieved ≥ 30% and ≥ 50% improvement, respectively, for IDEEL	Hypertension	Intentional overdose

Table 5 (continued)

References	Study type	Patients enrolled	Acthar dosing	Key efficacy outcomes	Common AEs in the Acthar group (≥ 3% frequency)	Serious AEs
Toyos et al., 2022 [58]	Phase IV open-label pilot study of dry eye disease	15	80 U twice weekly for 12 weeks	Significantly reduced corneal SPK lesions at days 14 ($p=0.0250$) and 84 ($p=0.0240$); decline in SANDE scores (62.0 at baseline vs. 46.9 at day 84); erythema ($p=0.0046$), IOP ($p=0.0052$), and conjunctival lissamine green staining ($p=0.0317$) each improved after 12 weeks of Acthar therapy compared with baseline	Injection site reaction ($n=2$), heart palpitations ($n=1$), insomnia ($n=1$), irritability ($n=1$), edema ($n=1$), headache ($n=1$), and upper respiratory infection ($n=1$)	Dysfunctional uterine bleeding ($n=1$)
Sharon et al., 2022 [59]	Medical records review of ocular mucous membrane pemphigoid	15	80 U twice weekly; mean treatment duration 21 months	No change in conjunctival scarring (Foster stage) for any patient; disease activity was well controlled for all 9 patients who remained on Acthar through last follow-up	1 patient experienced weight gain, elevated blood pressure, and headaches	None reported

AEs adverse events, *IDEEL* Impact of Dry Eye on Everyday Life, *IOP* intraocular pressure, *MS* multiple sclerosis, *NA* not applicable, *RL* response level, *RVSS* Retinal Vasculitis Severity Scoring, *SANDE* Symptom Assessment in Dry Eye, *SPK* superficial punctate keratitis

[a]Described as treatment-related or study drug-related

Table 6 Clinical and real-world evidence studies of Acthar in sarcoidosis

References	Study type	Patients enrolled	Acthar dosing	Key efficacy outcomes	Common AEs in the Acthar group (≥3% frequency)	Serious AEs
Baughman et al., 2016 [60]	Chart review/pilot study	47	80 U twice a week	11/29 (38%) patients who completed at least 3 months of Acthar had disease improvement; 17/19 patients taking prednisone had their dosage reduced >50% following Acthar therapy	Not reported	Anxiety/agitation ($n=3$), cryptococcal infection ($n=2$), peripheral edema ($n=2$), injection site pain ($n=1$), weakness ($n=1$), worsening disease ($n=1$), and allergic reaction to injection ($n=1$); 1 death due to neurosarcoidosis and 1 death due to pulmonary disease
Baughman et al., 2017 [61]	Single-blind trial	16	80 U daily for 10 days followed by randomization to 40 or 80 U twice weekly for 24 weeks	Acthar led to a significant reduction in prednisone dose within 7 weeks ($p=0.0156$), which persisted for 24 weeks ($p=0.0078$) of the study; a lower dose (40 U) was as effective as 80 U	Anxiety and fluid retention on the day of drug administration ($n=8$)	None reported
Chopra et al., 2019 [62]	Medical records analysis	302	Individualized Acthar dose regimens	Mean duration of Acthar (32.5 weeks); corticosteroid use decreased from 61.3% to 12.9%; overall status and symptoms improved in 95% and 73% of patients, respectively	NA	NA

Table 6 (continued)

References	Study type	Patients enrolled	Acthar dosing	Key efficacy outcomes	Common AEs in the Acthar group (≥3% frequency)	Serious AEs
Mirsaeidi et al., 2023 [65]	Phase IV RCT	55	80 U twice weekly for 24 weeks of a double-blind phase followed by an optional 24-week open-label extension	Double-blind phase, Acthar vs. placebo: glucocorticoid tapering, percentage change from baseline (95% CI) −57.3% (−71.2 to −43.4) vs. −58.6% (−70.5 to −46.7); lung FVC improvement ≥5%, *n* (%): 10 (37%) vs. 7 (25%); lung DLCO improvement ≥5%, *n* (%): 5 (18.5%) vs. 4 (14.3%); KSQ mean percentage change from baseline (SD; 95% CI): 9.43% (39.2; −5.4 to 24.2) vs. 2.3% (27.7; −10.9 to 15.5); STS, mean (SD; 95% CI): 1.4 (2.2; 0.5 to 2.3) vs. 0.7 (2.3; −0.2 to 1.6) Open-label extension, continued on Acthar vs. switched from placebo to Acthar: glucocorticoid tapering, percentage change from baseline (95% CI): −75.7% (−90.5 to −60.95) vs. −70.1% (−86.6 to −53.6); lung FVC improvement ≥5%, *n* (%): 2 (12.5%) vs. 6 (30.0%); lung DLCO improvement ≥5%, *n* (%): 9 (56.3%) vs. 6 (30.0%); KSQ mean percentage change from baseline (SD; 95% CI): 1.46% (39.2; −17.7 to 20.7) vs. 4.22% (33.4; −9.8 to 18.2); STS, mean (SD; 95% CI): 1.8 (2.0; 0.8 to 2.8) vs. 0.9 (2.2; −0.1 to 1.9)	Fatigue (*n* = 8), peripheral edema (*n* = 5), injection site bruising (*n* = 5), upper respiratory tract infection (*n* = 6), bronchitis (*n* = 4), pneumonia (*n* = 1), arthralgia (*n* = 5), back pain (*n* = 2), cough (*n* = 7), dyspnea (*n* = 4), dizziness (*n* = 3), headache (*n* = 5), nausea (*n* = 6), gastrointestinal reflux (*n* = 4), diabetes mellitus (*n* = 8), contusion (*n* = 3), and sarcoidosis (*n* = 4)	Uveitis (*n* = 1), cholelithiasis (*n* = 1), influenza (*n* = 1), asthma (*n* = 1), pneumonia (*n* = 1), and gastrointestinal hemorrhage (*n* = 1)

AEs adverse events, *CI* confidence interval, *DLCO* diffusing capacity of the lungs for carbon monoxide, *FVC* forced vital capacity, *KSQ* King's Sarcoidosis Questionnaire, *NA* not applicable, *RCT* randomized controlled trial, *SD* standard deviation, *STS* sarcoidosis treatment score

3.10 Ocular Mucous Membrane Pemphigoid

A chart review evaluated treatment with Acthar in patients with refractory ocular mucous membrane pemphigoid that did not respond to immunomodulatory drugs. Acthar treatment for 21 months was associated with controlled disease and was considered a viable alternative or adjunctive therapy, with no serious drug-related AEs observed (Table 5) [59].

3.11 Sarcoidosis

Among patients with sarcoidosis who were treated with Acthar for 3 months or longer in a chart review study, 38% experienced significant clinical improvement and 89% who were receiving prednisone at initiation of treatment had their prednisone doses reduced by more than 50% [60]. Of the patients who began the study, 23% discontinued due to drug toxicity [60]. A multicenter, single-blind trial of chronic pulmonary sarcoidosis noted a significant decrease in prednisone dose as well as improvements in diffusing capacity of the lungs for carbon monoxide, King's Sarcoidosis Questionnaire general health status, and Fatigue Activity Scale score in patients who completed 24 weeks of Acthar treatment [61].

An analysis of medical records from patients with sarcoidosis treated with Acthar indicated that it was a viable treatment for advanced sarcoidosis, with overall status improvement in 95% of patients. The percentage of patients using corticosteroids was reduced from 61.3% at initiation of Acthar to 12.9% after 3 months of therapy (Table 6) [62].

A Delphi study on the management of Acthar for pulmonary sarcoidosis made key recommendations, including an initial Acthar regimen at a lower dose (40 U) twice weekly for less severe disease, followed by an individualized maintenance dose for responders [63]. However, the panelists were unable to reach a consensus on whether a higher initial Acthar dose should be used for more severe disease [63]. In addition, the use of concomitant steroids should quickly be tapered, and guidance for AE management was presented. Furthermore, a recent narrative review provided a detailed overview of the clinical guidelines, mechanism of action, efficacy, and safety of Acthar in the treatment of pulmonary sarcoidosis [10].

PULSAR, a recently completed phase IV exploratory clinical trial for pulmonary sarcoidosis, examined efficacy endpoints such as steroid tapering, pulmonary function tests, lung imaging, patient-reported outcomes, and a novel composite sarcoidosis treatment score during 48 weeks of Acthar therapy [64, 65]. The study showed trends in efficacy data that suggested greater improvements with Acthar compared with placebo, including faster discontinuation of corticosteroids [65].

3.12 Nephrotic Syndrome

Substantial improvement was noted for patients with nephrotic syndrome due to idiopathic membranous nephropathy who were treated with Acthar in a phase Ib/II open-label, dose-finding study. By 12 months of follow-up, significant reductions in proteinuria and improvements in serum albumin and cholesterol levels were observed, with increased improvements associated with higher cumulative Acthar dose and no significant AEs reported [66].

In a case series of nephrotic syndrome due to various etiologies, Acthar treatment was associated with proteinuria reduction of 30% or greater in more than 80% of patients. About 16% of patients discontinued the treatment due to AEs that included weight gain, hypertension, edema, fatigue, and seizures [67].

In another case series, 53.8% of patients with nephrotic syndrome due to minimal change disease or focal segmental glomerulosclerosis showed a complete or partial response to Acthar as assessed by reductions in protein-to-creatinine ratio. Five patients from the focal segmental glomerulosclerosis group exhibited steroid-like adverse effects, which resulted in the discontinuation of 2 patients from Acthar therapy [68].

The safety and efficacy of Acthar alone or in combination with tacrolimus for focal segmental glomerulosclerosis or membranous nephropathy were examined in a prospective, open-label trial. Proteinuria was significantly reduced after 6 months with Acthar alone. In patients with no response or partial response to Acthar, an additional 6-month treatment with a combination of Acthar and tacrolimus improved the clinical response compared with Acthar alone. All patients completed at least 6 months of therapy and none required discontinuation of Acthar [69].

In a chart-review study, Acthar for the treatment of focal segmental glomerulosclerosis following kidney transplant was evaluated in patients who had received donor kidneys. Complete or partial remission of focal segmental glomerulosclerosis was observed in 36% of patients after receiving Acthar therapy for 6 to 24 months. No patients discontinued Acthar due to AEs [70].

An open-label pilot study of immunoglobulin (Ig) A nephropathy found significantly reduced proteinuria, stable glomerular filtration rate, and increased serum albumin in patients with severe disease at 12-month follow-up following 6 months of Acthar treatment. AEs included 2 viral infections (1 herpes zoster, 1 upper respiratory tract) and 4 bacterial infections (2 sinusitis, 1 pneumonia, 1 otitis media) (Table 7) [71].

Table 7 Clinical and real-world evidence studies of Acthar in nephrotic syndrome

References	Study type	Patients enrolled	Acthar dosing	Key efficacy outcomes	Common AEs in the Acthar group (≥3% frequency)	Serious AEs
Hladunewich et al., 2014 [66]	Phase Ib/II pilot study of idiopathic membranous nephropathy	20	40 or 80 U twice weekly up to 24 weeks	Significant decrease in mean proteinuria, increase in serum albumin, and improvement of cholesterol profile ($p \leq 0.001$) at 12-month follow-up; complete or partial remission in 12/20 patients	None reported	None reported
Madan et al., 2016 [67]	Case series including idiopathic focal segmental glomerulosclerosis, idiopathic membranous nephropathy, IgA nephropathy, diabetic nephropathy, systemic lupus erythematosus class V membranous lupus nephritis, minimal change disease, membranoproliferative glomerulonephritis, and fibrillary glomerulonephritis	44	80 U twice weekly	Complete or partial remission in 23/37 (62.2%) patients; clinical response to Acthar in 30/37 (81.1%) patients	Weight gain ($n=7$)[a], hypertension ($n=4$)[a], and hyperglycemia ($n=4$)[a]	None reported
Filippone et al., 2016 [68]	Case series of nephrotic syndrome secondary to minimal change disease or focal segmental glomerulosclerosis	13	Individualized/variable	7/13 patients had a complete ($n=3$) or partial ($n=4$) response	Weight gain ($n=4$), myalgia ($n=2$), worsening diabetes ($n=2$), increased skin pigmentation ($n=2$), hypertension ($n=2$), edema ($n=1$), and fatigue ($n=1$)	None reported
Tumlin et al., 2017 [69]	Prospective observational study of membranous glomerulopathy and focal segmental glomerulosclerosis	22	40–80 U 2–3 times per week for 6 months followed by addition of tacrolimus for an additional 6 months for patients exhibiting no or partial response	Tacrolimus/Acthar combination increased the number of complete and partial responses compared with Acthar alone in both the MGN (CR: 25.0% vs. 0.0%; PR: 75.0% vs. 44.0%) and FSGS (CR: 17.0% vs. 7.7%; PR: 66.0% vs. 62.0%) groups	Hyperglycemia ($n=5$), insomnia ($n=2$), and lower extremity edema ($n=3$)	None reported
Grafals and Sharfuddin, 2019 [70]	Chart review of focal segmental glomerulosclerosis with a history of kidney transplant	14	80 U twice weekly for up to 24 months	Complete or partial remission of FSGS in 5 (36%) patients	Swelling/edema ($n=2$), fatigue ($n=1$), diabetes ($n=1$), hyperglycemia ($n=1$), and weight gain ($n=1$)	None reported

Table 7 (continued)

References	Study type	Patients enrolled	Acthar dosing	Key efficacy outcomes	Common AEs in the Acthar group (≥ 3% frequency)	Serious AEs
Zand et al., 2020 [71]	Open-label pilot study of IgA nephropathy	19	80 U twice weekly for 6 months	Statistically significant improvement of proteinuria ($p = 0.007$) and increase in serum albumin ($p = 0.02$) observed at 12-month follow-up; no significant change in eGFR; 8 (42%) partial remissions and 0 complete remissions	Muscle soreness (4 events)[a], injection reaction (7 events)[a], acne (3 events)[a], anxiety (3 events)[a], hot flashes (3 events)[a], insomnia (3 events)[a], hypertension (2 events)[a], sinusitis (2 events)[a], pneumonia (1 event)[a], otitis media (1 event)[a], shingles (1 event)[a], viral URI (1 event)[a], increased appetite (1 event)[a], polycythemia (1 event)[a], and face roundness (1 event)[a]	None reported

AEs adverse events, *CR* complete response, *eGFR* estimated glomerular filtration rate, *FSGS* focal segmental glomerulosclerosis, *IgA* immunoglobulin A, *MGN* membranous glomerulopathy, *PR* partial response, *URI* upper respiratory infection.

[a]Described as treatment-related or study drug-related

4 Conclusions

Acthar has a long-standing history of treatment of autoimmune and other inflammatory disorders, with extensive clinical data confirming its safety and efficacy in many therapeutic areas. Early-phase clinical and preclinical studies have supported a distinct mechanism of action compared with standard of care therapies. Mallinckrodt Pharmaceuticals has conducted more than 20 preclinical mechanistic studies of Acthar and initiated 8 clinical studies with a targeted combined enrollment of approximately 900 patients [29]. In addition, the use of Acthar has been the subject of more than 500 published manuscripts and abstracts to date [29]. The results of these studies support the safety and efficacy of Acthar in patients with inflammatory diseases for whom standard treatments have become ineffective or are associated with intolerable adverse effects.

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Declarations

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