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Clinical Features, Outcomes, and Response to Corticosteroid Treatment of Acute Tubulointerstitial Nephritis: A Single-Centre Retrospective Cohort Study in the Czech Republic

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Keywords
Acute kidney injury · Acute tubulointerstitial nephritis · Corticosteroid treatment · Outcome · Renal biopsy

Abstract
Introduction: Acute tubulointerstitial nephritis (ATIN) is a well-recognized cause of acute kidney injury (AKI) due to the tubulointerstitial inflammation. The aim of this study was to explore the clinical features, outcomes, and responses to corticosteroid treatment in patients with ATIN. ***Methods:*** Patients with biopsy-proven ATIN, who were diagnosed between 1994 and 2016 at the Department of Nephrology, Charles University, First Faculty of Medicine, and General University Hospital in Prague, were included in the study. Patient demographics, the aetiological and clinical features, the treatment given, and the outcome at 1 year of follow-up were extracted from patient records. ***Results:*** A total of 103 ATIN patients were analysed, of which 68 had been treated with corticosteroids. There was no significant difference in the median serum creatinine 280 (169–569) μmol/L in the conservatively managed group versus 374 (249–558) μmol/L in the corticosteroid-treated group, $p = 0.18$, and dependence on dialysis treatment at baseline at the time of biopsy (10.3 vs. 8.6%). During the 1 year of follow-up, those ATIN patients who had been treated with corticosteroids did better and showed greater improvement in kidney function, determined as serum creatinine difference from baseline and from 1 month over 1-year period ($p = 0.001$). ***Conclusions:*** This single-centre retrospective cohort study supports the beneficial role of the administration of corticosteroid therapy in the management of ATIN.

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Introduction

Acute tubulointerstitial nephritis (ATIN) is an immune-mediated cause of acute kidney injury (AKI) characterized by the presence of inflammatory cell infiltrate in the tubules and interstitium of the kidney [1]. According to the Czech Registry of Renal Biopsies (CRRB), tubulointerstitial nephritis (TIN) was diagnosed

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in 4% of all native renal biopsies performed in the Czech Republic from 1994 to 2016.

The nationwide CRRB was founded in 1994 and currently comprises thirty-one Czech nephrology centres performing native kidney biopsies. The CRRB collects the histopathological, basic clinical, and essential laboratory data. The CRRB provides a unique platform to study the epidemiology of kidney diseases based on the histopathological diagnoses in the Czech Republic. This collected data from the CRRB enabled us to identify subjects with a histopathology diagnosis of TIN from 1994 until 2016. This set from the CRRB included 489 biopsy-proven TIN adult kidney biopsies. Subsequently, we identified 110 adult subjects with biopsy-proven ATIN at our centre and retrospectively analysed data from 103 of them.

The aetiologies of ATIN are various and mostly include drugs, accounting for more than half of the cases, followed by infections, systemic diseases, and idiopathic with no identified cause [2, 3]. In recent years, a higher frequency of cases of ATIN has been reported among the subjects receiving immune checkpoint inhibitors [4].

The clinical presentation of ATIN may reflect the hypersensitivity reaction in drug-induced cases with fever, skin rash, joint involvement, low-grade proteinuria, erythrocyturia, and eosinophiluria [5]. However, these clinical features are not found in all patients. Patients with ATIN of any cause may present with non-specific patterns of AKI, and many patients have no symptoms [6]. In addition, ATIN may be accompanied by oliguria or gross haematuria [7]. Severe tubulointerstitial damage can result in the need for renal replacement therapy (RRT). The initial inflammatory infiltration of the interstitium by lymphocytes, macrophages, and plasma cells may later develop into interstitial fibrosis (IF) and tubular atrophy (TA). These patterns of tubulointerstitial changes may further progress to chronic kidney disease (CKD) and even terminal renal failure [8].

Renal biopsy determines the correct diagnosis, evaluates the severity of the kidney damage, and imparts the treatment strategies. The main histopathological features are oedema and inflammatory infiltration of the interstitium, with abundant lymphocytes, plasmocytes, and eosinophils. Tubulitis and early fibrosis can be present as well as granulomas.

In previous retrospective studies, corticosteroids were mostly used or were recommended to be used for ATIN [9–11]. However, other studies showed no effect of steroid therapy on the outcome of ATIN [5, 12–14]. The role of corticosteroid treatment for ATIN thus remains controversial. The aim of this single-centre retrospective cohort study was to evaluate the clinical features, treatment options, and outcomes of patients with biopsy-proven ATIN.

Materials and Methods

We performed a retrospective cohort data analysis of patients with biopsy-proven TIN. Firstly, 489 adult patients with biopsy-proven TIN presenting between January 1994 and December 2016 were identified from the CRRB. Subsequently, 110 patients with biopsy-proven ATIN in the period from 1994 until 2016 were identified at our centre, the Department of Nephrology, First Faculty of Medicine, Charles University, and General University Hospital in Prague. Seven patients were excluded: individuals younger than 18 years of age at the time of biopsy, those with bacterial TIN, or those with a history of CKD. Subsequently, we retrospectively analysed 103 ATIN patients all of whom had fulfilled at least 12 months of follow-up from initial presentation (Fig. 1).

Parameters Investigated

A review of patient case records was made, and the data were analysed to determine patient demographics, clinical features, and histopathological renal biopsy characteristics. Possible trigger factors including drugs, systemic autoimmune disorders, infectious, toxic substances, and cases idiopathic in origin were identified. The mode of treatment and response to corticosteroid treatment were recorded. Patients were considered as dialysis-dependent if they had entered RRT within 7 days of the kidney biopsy. The presence of eosinophilia, erythrocyturia, leukocyturia, 24-h proteinuria, haemoglobin, and serum creatinine were measured using standard laboratory methods and then recorded. Comorbidities, e.g., a history of hypertension or diabetes mellitus, in addition to clinical features such as a rash or fever, were also documented for each patient.

Histopathological Evaluation

The renal biopsy specimens were processed for light microscopy, immunofluorescence examination, and electron microscopy. The diagnosis of ATIN was made with the presence of inflammatory interstitial infiltrate, the presence or absence of interstitial oedema and eosinophils, TA, and the absence of acute glomerular disease. The percentage of IT was also evaluated. The presence of large proportion of polymorphonuclear leukocytes, signs of CKD with a high degree of tubulointerstitial fibrosis, and glomerulosclerosis were considered as exclusion criteria.

Treatment

The decision to use corticosteroid therapy was made by the nephrologist caring for the patient at the time of the renal biopsy. The therapy was especially initiated in patients with higher serum creatinine, eosinophilia, and more active urinary sediment. The dose and duration of corticosteroid treatment were recorded. The patients were treated using either i.v. pulses of 250–500 mg of methylprednisolone for 3 days followed by oral 0.75 mg/kg or using directly oral prednisone 1 mg/kg/day tapered over 6–12 weeks. In those patients who received steroids, treatment was initiated within 1–4 days of the renal biopsy. The conservative treatment of ATIN included general principles of the management of AKI: discontinuation of the culprit drug therapy, optimal hydration to optimize the volume status and the perfusion pressure, the correction and avoidance of hyperglycaemia, maintenance of the normotension, and the adequate treatment of hypertension. These general measures of the AKI treatment were applied to both studied groups.

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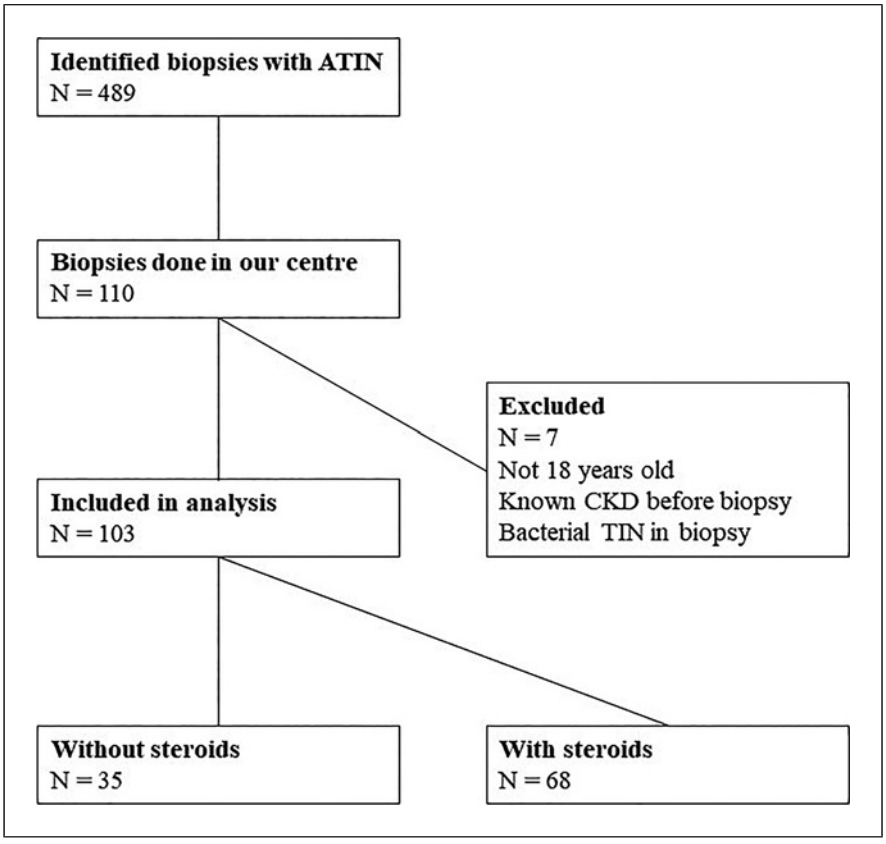

Fig. 1. Flowchart of patient selection for the study. ATIN, acute tubulointerstitial nephritis; CKD, chronic kidney disease; TIN, tubulointerstitial nephritis.

The response to treatment was assessed using both the absolute values of serum creatinine or estimated glomerular filtration rate (eGFR) and the relative change from the patient's baseline. The time-points were the time of biopsy (baseline), 1 month, and 12 months (last parameter recorded for each patient) of follow-up. Dialysis dependence was also recorded.

Statistical Analysis

Results are shown as mean ± standard deviation for continuous variables. If the data were not normally distributed, median values with interquartile ranges are shown. For categorical variables, the number affected/total (percentage) were used. Quantitative variables were compared using the *t*-test or Kruskal-Wallis test for non-skewed variables. A *p value* <0.05 was considered significant.

Results

In total, 103 adult patients, 52 male and 51 female, were diagnosed with ATIN confirmed by renal biopsy. The demographic, clinical, laboratory, and histopathological features of the patients are shown in Table 1.

Thirty percent of the patients had a definitive history of taking a culprit drug. Table 2 depicts the aetiological factors, which were autoimmune diseases, parainfectous processes, and toxins (as assessed by the attending nephrologist). 51.4% of the patients were considered idiopathic with no evidence of the underlying disease or intake of chemical substance. The drug-induced ATIN cases (n = 31) included those caused by non-steroidal anti-inflammatory agents n = 7 (22%), proton pump inhibitors n = 1 (3%), chemotherapeutic agents n = 2 (7%), narcotics n = 2 (7%), antibiotics n = 18 (58%), and Chinese herbs n = 1 (3%).

As shown in Table 1, the patients were divided into two groups: those treated using corticotherapy and those undergoing conservative treatment. No significant differences in age, sex, comorbidities, or baseline kidney function were observed between those two groups. There were no differences between the baseline serum creatinine level or the eGFR of the two groups. However, at baseline, patients on conservative treatment had higher proteinuria in comparison with patients on corticotherapy as well as protein/creatinine urine ratio. At the end of the follow-up, the medians of the protein/creatinine ratios were not different between the two groups. There were no differences in the other

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Table 1. Demographics, clinical presentation, laboratory, and histopathological features of evaluated patients

	Total (n = 103)	Conservatively managed (n = 35)	Corticosteroid-treated (n = 68)	p value conservative versus corticosteroid
Demographic features				
Age, years, median (range)	53 (36.6–64.0)	52.2 (40.2–61.1)	54.0 (36.1–65.4)	0.84
Male/female ratio	52/51	21/14	31/37	0.65
Clinical features				
AKI, %	70.8	57.1	77.9	0.56
Hypertension, %	52.4	62.8	47.0	0.24
Diabetes mellitus, %	11.6	2.9	16.2	0.74
Rash, %	6.8	8.6	5.9	0.76
Fever, %	17.5	17.1	17.6	0.82
Laboratory features				
Eosinophilia, %	16.5	5.7	22.1	0.24
Active urinary sediment, %	82.5	77.1	85.3	0.64
Leukocyturia, %	50.4	40	55.9	0.51
Erythrocyturia, %	52.4	45.7	55.9	0.82
Proteinuria, g/24 h	0.59 (0.31–1.32)	1 (0.48–2.56)	0.51 (0.31–0.98)	0.03
Protein/Creatinine ratio, mg/mmoL, median (range)	0.09 (0.05–0.15)	0.12 (0.06–0.27)	0.08 (0.04–0.13)	0.04
Haemoglobin, g/L, median (range)	101 (97–113)	106 (99–114)	102 (97–115)	0.56
Serum creatinine, μmol/L, median (range)	360 (229–564)	280 (169–569)	374 (249–558)	0.18
eGFR, mL/min/1.73 m^2, median (range)	12.4 (7.4–20.8)	16.6 (7.4–30.3)	11.7 (7.5–17.9)	0.16
Histopathological features				
Interstitial fibrosis, % (range)	20 (15–40)	30 (20–40)	20 (15–30)	0.06
Severe tubulointerstitial inflammation, % (range)	30 (30–40)	30 (30–30)	30 (30–40)	0.24

Table 2. Aetiological factors in ATIN (as assessed by the attending nephrologist)

Aetiology	n (%)
Autoimmune	10 (6.8)
Idiopathic	53 (51.4)
Parainfectious	4 (3.9)
Drug-induced	31 (30)
Toxic	5 (4,8)
Total	103 (100)

laboratory parameters, e.g., neither in eosinophilia, leukocyturia, or erythrocyturia nor in clinical presentation (fever, rash, hypertension) in both groups. Eleven patients had diabetes in the corticosteroid-treated group at the baseline which did not change at the end of the follow-up. At the end of the follow-up, there was a non-significant trend of a lower median serum creatinine in patients on corticotherapy versus those conservatively managed. Table 3 illustrates the changes in serum creatinine over a 1-year period for the conservatively managed group, in comparison with the corticosteroid-treated group.

Two regimes of corticotherapy treatment were also analysed: corticosteroid pulses (n = 12) versus oral corticosteroid treatment only (n = 56), and there were no significant differences in the outcome as after 1 month, the median serum creatinine was 238 (150.2–300.5) μmol/L versus 229 (159.1–353.6) μmol/L, p = 0.39. At 12 months of follow-up, the median serum creatinine was 132 (99–167) μmol/L versus 151 (98–238) μmol/L, p = 0.25.

The severity of kidney dysfunction at presentation is illustrated by the fact that 10 (9.7%) of the cases were dialysis dependent at the time of biopsy or required dialysis treatment within 1 week of the biopsy. After 1 month, 17 (16.5%) of the cases were dialysis dependent, and at the end of the follow-up, 9 (8.7%) patients were on chronic replacement therapy. In the corticosteroid-treated group, 7 (10.3%) of the cases required dialysis at the time of biopsy, five of them eventually regained

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Table 3. Serum creatinine over 1-year period in the conservatively management versus the corticosteroid-treated group

	Conservatively managed (n = 35)	Corticosteroid-treated (n = 68)	p value
Baseline	280 (169–569)	374 (248–558)	0.18
1 month	221 (132–416)	236 (167–336)	0.90
12 months	230 (113–306)	153 (95–282)	0.09

Values for serum creatinine (μmol/L) are given as median (interquartile range).

independent kidney function. In additional four patients, dialysis was initiated within 1 month of the corticosteroid treatment, so 6 patients (8.8%) were on dialysis after 1 month of the treatment. However, three of them had partial recovery, and only 3 (4.4%) of the cases were in need of chronic RRT at the end of the follow-up.

In the conservatively treated group, 3 (8.6%) patients were in need of dialysis at the time of biopsy, but all of them were independent of dialysis after 1 month. However, additional 11 patients (31.42%) had to start dialysis within 1 month, and 6 of them (17.2%) remained on chronic RRT at the end of the follow-up. There was a trend of a higher need of acute dialysis and chronic RRT at the end of follow-up in the conservatively managed group versus patients on corticotherapy. Patients treated with corticosteroids were more likely to recover independent kidney function.

The corticosteroid treatment group showed more improvement in serum creatinine from the baseline to 1 month and 12 months than the conservatively treated group. Table 4 describes the dynamics of serum creatinine differences.

Table 4. Kruskal-Wallis test p values for serum creatinine difference between prespecified time-points (baseline, 1 month, and 12 months) in the conservatively management and the corticosteroid-treated groups

p value	Conservatively managed (n = 35)		Corticosteroid-treated (n = 68)	
	1 month	12 months	1 month	12 months
Baseline	0.21	0.09	<0.0001	<0.0001
1 month	–	0.66	–	0.0012

Discussion

Even though ATIN is an important cause of AKI, its pathophysiology, treatment, and outcomes are not yet fully understood. The present single-centre retrospective cohort study analysed clinical features, outcomes, and the effect of corticosteroid therapy in patients with idiopathic, drug-induced, autoimmune, parainfectious, and toxic ATIN. The different range of aetiologies between different cohorts probably explains the various outcomes of ATIN in the studied populations [3, 14, 15]. Our results confirm the positive effect of corticosteroid therapy on renal outcomes.

ATIN is characterized by the presence of tubulointerstitial inflammation and oedema, leading to an acute deterioration in kidney function. In this and previous studies, ATIN accounts for 1–4% of all kidney biopsies [1, 13, 16]. The prevalence of ATIN has increased in recent years, particularly in the elderly, but remains very rare in children [16, 17]. The real incidence of ATIN might be underestimated because not all patients with suspected ATIN undergo a kidney biopsy but are treated empirically. Due to the rising awareness of drug-induced ATIN in the clinical setting, early withdrawal of the offending drug may lead to recovery without the need for a kidney biopsy. AKI may precede systemic manifestations in autoimmune-related ATIN, leading to misdiagnosis [15]. There may also be patients in whom the disease is not diagnosed due to the paucity of symptoms, lack of a laboratory examination, and the self-limiting course once the cause has been terminated.

The clinical features of the patients in this study included AKI, leukocyturia, non-nephrotic proteinuria, and microscopic haematuria similar to those reported in other studies of ATIN patients [5, 9, 16]. A recent study highlighted that haematuria is common in ATIN and that it is linked with the parameters of disease severity and worse kidney outcomes [18]. Analysis of the data also showed a high percentage of ATIN patients with hypertension, emphasising possible deleterious vessel changes which accompany the development of kidney injury in ATIN patients. It has been suggested that the

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hypertension might be attributed to the vascular changes in the population of subjects with a higher age [16]. Thus, in AKI with altered urinary sediment, proteinuria, and hypertension, a renal biopsy provides an essential diagnosis of histopathology, probable pathogenesis, as well as some clues for prognosis [19, 20]. It might also be helpful in distinguishing those more appropriate for corticosteroid treatment.

We performed a retrospective study of ATIN patients with a follow-up of 12 months. The overall features of cases treated using corticosteroids and conservatively managed were comparable at the baseline. During the 1 year of follow-up, the patients treated with corticosteroids had better outcomes and showed significant improvement of kidney function, whereas in the conservatively managed group, the improvement of kidney function was not statistically significant. In addition, some patients became dialysis-independent during the follow-up, supporting the benefit of using corticosteroids for the treatment of ATIN patients.

Our data highlighted the incidence of histologically proven ATIN in our centre, with more than half of the cases as idiopathic and more than a quarter drug-induced. The majority of cases that presented with AKI were treated with corticosteroid treatment. Patients with more severe AKI were treated with corticosteroids more frequently. In addition, the severity of IF and TA in those patients treated conservatively tended to be more pronounced than in those patients who received corticosteroids. The severity of IF/TA has been previously shown as the main prognostic factor in the outcome of ATIN [7], which might partly explain the favourable effect of corticosteroid treatment in our study. However, it may also show an uneven indication for treatment, with patients who have poor prognostic markers at baseline being treated less frequently.

There are inconsistent results from retrospective cohorts with some studies presenting the beneficial role of the corticosteroid therapy of ATIN [9–11, 21], whereas other studies showed no effect of corticosteroid treatment [5, 13, 14, 22]. A short course of corticosteroid therapy, in addition to withdrawal of the suspected chemotherapy agent, has been advocated to treat ATIN in cancer patients [23]. It appears that the immune checkpoint inhibitor-induced ATIN responds well to corticosteroid treatment, resulting either in complete recovery of kidney function or at least partial recovery [4, 24, 25]. Nevertheless, corticosteroids are generally used for treating ATIN [3, 9, 10, 26, 27].

The different efficacy of corticosteroid therapy might be attributed to the different percentage of aetiologies being mostly drug-induced, and the various baseline eGFRs in previous studies. On the one hand, the studies by Gonzalez et al. [9], Raza et al. [10], and Prendecki et al. [11] presented mostly a population with drug-induced ATIN timely treated with corticosteroids which resulted in better kidney function with fewer patients requiring RRT. The study by Fernandez-Juarez et al. [28] showed that after the withdrawal of the causing drug, early treatment with corticosteroids resulted in an increasing rate of recovery of renal function in drug-induced ATIN. A randomized controlled trial revealed an even efficacy of oral and pulse corticosteroids, resulting in a remission at 3 months after biopsy in twenty-nine cases of drug-induced ATIN [29]. On the other hand, studies by Yun et al. [14], Clarkson et al. [5], Valluri et al. [13], and Muriithi et al. [22] showed no benefit of the corticosteroid therapy in the drug-induced ATIN population. The patients treated with corticosteroids in these series suffered from more severe AKI and a lower baseline eGFR.

Although the results of our study support the benefits of the corticosteroid therapy on the renal outcome of ATIN, there were some limitations. The present study was a retrospective single-centre cohort study. The decision to treat with corticosteroids or not was made by a clinician with no defined protocol of corticosteroid usage. Retrospectively, we suppose that the baseline kidney dysfunction and diabetes status were mostly the confounding factors that affected a clinician's choice of whether or not to use corticosteroids. Additionally, the studied groups were heterogeneous with mostly idiopathic ATIN but also with a significant proportion of drug-induced cases. The small number of subgroups according to the aetiology of ATIN did not allow for performing the statistical analysis based on the aetiology of ATIN. Nevertheless, all cases were evaluated by an experienced pathologist trained in renal histopathology which enabled us to predict the response to corticosteroid treatment based also on the degree of IF/TA.

Conclusion

The outcome of this cohort of ATIN patients within 1 year of follow-up has proven the beneficial use of corticosteroid treatment on the improvement of kidney function. Considering the results of this study, we support the concept that corticosteroid treatment should be initiated early and continued for at least 4–6 weeks [30]. Subsequent treatment should be guided according to the individual clinical performance of the patient. There is a continuous need for a multicentre, randomized,

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controlled trial to ultimately assess the effect, duration, and dosage of corticosteroids for the management of ATIN on long-term renal function to prevent CKD and the development of end-stage renal disease.

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Statement of Ethics

All patients have signed informed consent at the time of biopsy. This included sending their data to the registry and use of anonymized data for research. The study protocol was reviewed and approved by the Ethical Committee of the General University Hospital in Prague on February 16, 2023, approval number 6/23 S-IV.

Conflict of Interest Statement

O.Z., Y.C., E.J., D.M., D.F., T.I., V.K., and V.C.C. have no conflicts of interest to declare. R.R. has received consulting fees from AstraZeneca, Bayer, Astellas, and Boehringer Ingelheim. E.H. has received fees from Takeda and Servier. I.R. obtained lecturing fees from AstraZeneca CZ, Bayer CZ, Boehringer Ingelheim CZ, Eli Lilly CZ, Fresenius Medical Care CZ, Mundipharma CZ and is a member of the advisory board of AstraZeneca CZ, Boehringer Ingelheim CZ. V.T. obtained consultation fees from AstraZeneca, Bayer, Calliditas, Novartis, Omeros, Otsuka, and Travere.

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Author Contributions

O.Z. wrote the manuscript, extracted the data, contributed to the conception and design of the work, reviewed the data, contributed significant ideas to the content of the manuscript, reviewed the drafts, and reviewed and approved the final version of the manuscript. Y.C. extracted the data, contributed to the conception and design of the work, reviewed the data, reviewed the drafts, and reviewed and approved the final version of the manuscript. E.J. extracted the data, contributed to the conception and design of the work, reviewed the data, contributed significant ideas to the content of the manuscript, reviewed the drafts, and reviewed and approved the final version of the manuscript. R.R., D.M., D.F., T.I., I.R., and V.T. contributed to the conception and design of the work, reviewed the data, contributed significant ideas to the content of the manuscript, reviewed the drafts, and reviewed and approved the final version of the manuscript. E.H. reviewed the data, reviewed the drafts, and reviewed and approved the final version of the manuscript. V.K. provided statistical evaluation. V.C.C. wrote the manuscript, contributed to the conception and design of the work, reviewed the data, contributed significant ideas to the content of the manuscript, reviewed the drafts, and reviewed and approved the final version of the manuscript.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author. No supplemental files were created.

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