# Calcineurin inhibitors in the treatment of adult autoimmune hepatitis: a systematic review

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Original Article

# Calcineurin Inhibitors in the Treatment of Adult Autoimmune Hepatitis: A Systematic Review

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## Abstract

***Background and Aims:*** A considerable number of autoimmune hepatitis (AIH) patients completely or partially fail on first-line treatment. Several studies on the use of calcineurin inhibitors (CNIs) in the treatment of AIH have been published without focusing on indication. The aim was to assess the efficacy of CNIs in the treatment of adult AIH patients, specifically focusing on indication: first-line intolerant and with first-line insufficient response (failure to achieve or maintain remission), and with second versus third-line treatment. ***Methods:*** A literature search included studies on the use of CNIs in adult AIH. Patients with past or present use of CNIs from the Dutch AIH group cohort were added. The primary endpoint was biochemical remission while using CNIs. Secondary endpoints were biochemical response, treatment failure, and adverse effects. ***Results:*** Twenty studies from the literature and nine Dutch patients were included describing the use of cyclosporine in 59 and tacrolimus in 219 adult AIH patients. The CNI remission rate was 53% in patients with insufficient response to first-line treatment and 67% in patients intolerant to first-line treatment. CNIs were used as second-line treatment in 73% with a remission rate of 52% and as third-line treatment in 22% with a remission rate of 26%. Cyclosporine was discontinued in 13% and tacrolimus in 11% of patients because of adverse events. ***Conclusions:*** CNIs as rescue treatment in adult AIH patients are reasonably effective and safe both with insufficient response or intolerance to previous treatment. Prospective studies are needed.

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**Keywords:** Autoimmune hepatitis; Cyclosporine, Tacrolimus, Calcineurin inhibitor.

**Abbreviations:** 6-MP, 6-mercaptopurine; 6-TG, 6-thioguanine; AIH, autoimmune hepatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AZA, azathioprine; CNI, calcineurin inhibitor; CYC, cyclosporine; MMF, mycophenolate mofetil; PBC, primary biliary cholangitis; PRED, prednisolone; PSC, primary sclerosing cholangitis; TAC, tacrolimus.

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## Introduction

Autoimmune hepatitis (AIH) is characterized by hypergammaglobulinemia, autoantibodies and interface hepatitis.[1,2] Current first-line treatment consists of prednisolone (PRED) and azathioprine (AZA) leading to remission with acceptable side effects in most patients. However, a considerable number of all patients fail first-line treatment because of intolerable side effects or insufficient response (failure to achieve or maintain remission).[3] In noncirrhotic patients with intolerable side effects of PRED, budesonide is an excellent option.[3,4] For patients with intolerable AZA side effects 6-mercaptopurine (6-MP), 6-thioguanine (6-TG) or mycophenolate mofetil (MMF) are alternatives.[3,5–7] Patients with hepatotoxicity from AZA because of a skewed metabolism can be treated by adding allopurinol or switching to 6-TG.[7,8] There are a number of alternative therapies,[9] but many, like methotrexate, infliximab, rituximab, sirolimus, and everolimus, have been used as salvage treatments only in small case series.[10–14]

There is much more experience with the use of the calcineurin inhibitors (CNIs) cyclosporine (CYC) and tacrolimus (TAC) in AIH. In a real-world analysis, the reported use of MMF was most frequent, followed by CNIs.[9] Calcineurin inhibitors act through suppression of activated T cells via inhibition of the intracytoplasmic enzyme calcineurin, blocking nuclear transcription of proinflammatory cytokines such as interleukin-2.[15] Several systematic reviews were published focusing on the efficacy and safety of second and third-line immunosuppressive therapy for AIH in adults, including CNIs. However, interpretation of data was hampered by heterogeneity of outcome measures and dosing and the reason for conversion to a CNI differed.[16–21] The aim of this systematic review, which includes novel results of the Dutch national case series, was to assess the efficacy of CNIs in the treatment of adult AIH patients. We distinguished those

with intolerance for first-line treatment, those with insufficient response to first-line treatment, and patients with CNIs as second-line versus third-line treatment.

## Methods

### *Literature search*

A literature search of Medline, Embase, Web of Science, and the Cochrane database for relevant studies was performed using combinations of the terms "autoimmune hepatitis," "chronic active hepatitis," "calcineurin inhibitor," "cyclosporin," "ciclosporine," "Neoral," "tacrolimus." "Prograf," and "Advagraf." The exact search strategy is shown in supplemental PDF 1). The last search was performed in October 2021. Meeting abstracts were excluded. Reference lists of relevant studies were screened for appropriate articles.

### *Article selection*

Studies written in English, Dutch, German, or French describing the use of a CNI in the treatment of AIH patients 18 years of age or older and with sufficient data on treatment with CNIs were included. Treatment-naïve patients and patients with primary biliary cholangitis (PBC)[22] or primary sclerosing cholangitis (PSC)[23] variant syndromes before starting a CNI were excluded.

### *Data extraction*

The data extracted from the studies included the type of CNI, sample size, sex, age, disease duration before CNI, treatment duration before CNI, medications before CNI, reason for starting CNI (e.g. intolerance or insufficient response), line of treatment (i.e. second or third), dosage of CNI, dosing based on trough levels (i.e. yes or no, lower and upper limit), duration of CNI treatment, co-medication with CNI, adverse effects and result of CNI treatment (definitions see below), reasons for stopping CNI treatment and duration of follow-up after starting CNI. Authors were not contacted for missing data. Quality of the studies was assessed using the GRADE approach.[24]

### *Case series*

From the larger Dutch AIH group cohort, all patients with probable and definite AIH according to the international criteria, ≥18 years of age, and with past or present use of CNIs before April 2018 were included in the analysis.[2] The larger Dutch AIH group cohort in April 2018 consisted of over 1,300 patients with AIH and AIH variant (overlap) syndromes of all academic and large nonacademic centers in the Netherlands. Informed consent was obtained from each patient included in the study, and the study protocol conformed to the ethical guidelines of latest revision of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

### *Definitions*

Treatment failure, response, and remission were defined according to the 2019 AASLD guidelines.[25] As IgG and/or gamma globulin changes in articles were seldom reported after diagnosis and during treatment, they were not included in the definitions. Intolerance was stopping because of related side effects. Insufficient response was failure to achieve or maintain remission as determined by the treating physician or as stated in the articles. Treatment failure was a rise in, or stable aspartate aminotransferase (AST) and alanine aminotransferase (ALT) or intolerance. Biochemical response was a drop in AST and ALT below twice the upper limit of the reference or at least a 50% reduction in AST and ALT, without remission. Biochemical remission was normalization of AST and ALT. Efficacy of CNI treatment in the studies was reassessed according to the definitions as far as possible, which could lead to a discrepancy between the original study and results reported in this systematic review. Response to CNIs in the Dutch case series was determined by chart review. Follow-up was defined as time from starting CNI treatment until the last visit. Second-line treatment was defined as starting CNI treatment after treatment with corticosteroids with or without a thiopurine. Third-line treatment was defined as starting CNI after treatment with a second thiopurine, MMF or other immunosuppressants.

### *Endpoints*

The primary endpoint was biochemical remission while using CNI. The secondary endpoints were biochemical response or treatment failure while using CNI.

### *Statistical analysis*

Fisher's exact test, chi-square test for trend and the Mann-Whitney U test were used with $p < 0.05$ as the level of statistical significance. SPSS v.21 was used for the statistical analysis.

## Results

A total of 20 studies were identified and included in this systematic review. Eleven studies reported the use of CYC in 58 patients, and 11 report the use of TAC in 211 patients (Fig. 1).[15,26–44] Details of the GRADE scoring across the studies per outcome are summarized in Supplementary Table 1. The quality of the evidence was rated very low for all outcomes. From the Dutch AIH group cohort, nine patients with past or present use of CNI were identified. Eight were treated with TAC and one with CYC and are included in Table 1.

### *Cyclosporine*

Eleven studies described the use of CYC in 58 patients. Five were case reports[26–28,30,37] and six were case series.[15,29,31,32,43,44] In three case series, the patients treated with CYC were a portion of the entire case series. Data in these studies was variably reported for the entire case series, only the patients treated with CYC or only the pretreated patients.[15,32,44] In the Dutch cohort one patient using CYC was identified (Table 1). Taken together a total of 59 patients on CYC were described, 39 women (66%), 20 men (34%). Table 2 describes data on the initial treatment before starting CYC, and Table 3 describes data while on CYC treatment. In seven studies and the Dutch cohort, CYC dosage was adjusted based on through levels.[15,27–30,32,43] Overall 59% of the patients reached remission, 22% had a response without remission, 12% had treatment failure on CYC, and 7% of CYC treatment responses could not be de-

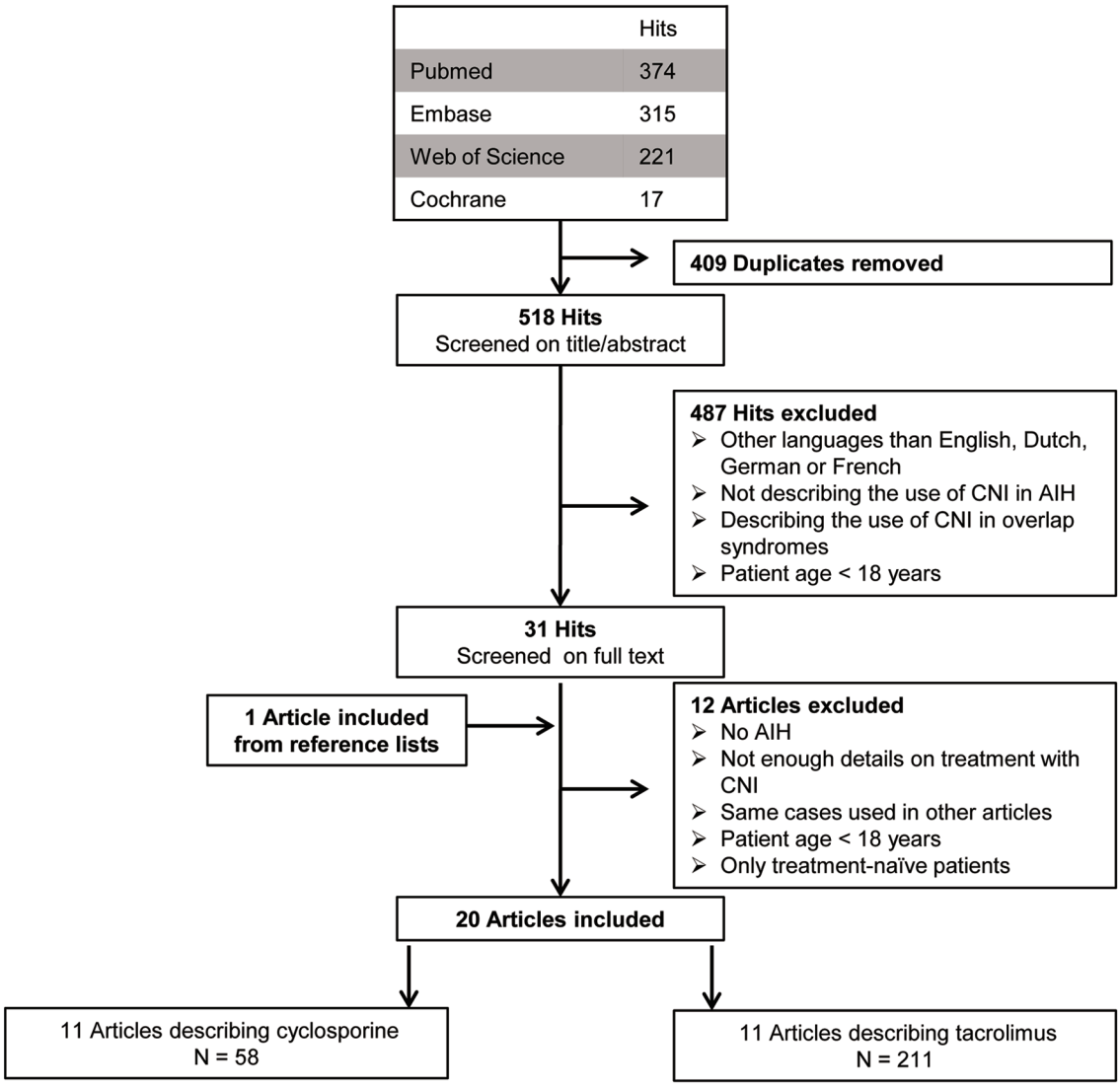


**Fig. 1. Flow chart of the literature search for the publications included in the systematic review.**

termined from the provided data. All 21 patients with known time to remission reached remission within 6 months after initiation of CYC. Treatment with CYC was discontinued in 32 patients (54%). Reasons for discontinuing were intolerable side effects in nine patients (15%), persistent remission in seven (12%), insufficient response in five (8%), and on the patient's own initiative in one (2%). In 10 patients, the reason for discontinuation could not be determined.

### *Cyclosporine: adverse effects*

In most studies, adverse effects were reported collectively, not per patient, and multiple adverse effects could occur in one patient. Supplementary Figure 1 shows the minimal number of patients per side effect reported. Eleven of the 87 patients (13%) discontinued CYC because of intolerable adverse effects, one with uncontrollable hypertension, one with paresthesia, one with bloody diarrhea, one with flu-like symptoms, one with kidney failure, one with thrombocytopenia. The reason was not reported in five patients.

### *Tacrolimus*

Eleven studies described the use of TAC in a total of 211 patients. One was a case report[39] and 10 were case series.[15,33–36,38,40–42,44] In five case series, the patients treated with TAC were a part of the entire case series. Data in these studies was variably reported for the entire case series or only for patients treated with TAC.[15,34,39,40,44] In the Dutch cohort, eight patients with past or present use of TAC were identified and are included in Table 1. Taken together a total of 219 AIH patients on TAC were described, including 151 women (69%) and 56 men (26%) The sex of 12 patients could not be determined.

Table 4 describes data on the initial treatment before starting TAC, and Table 5 describes data while on TAC treatment. In seven studies and the current Dutch case series, the TAC dosage was adjusted based on through levels.[15,33,35,36,38,41,42] Overall, 59% of the patients reached remission, 15% had a response without remission, and 14% had treatment failure on TAC. Twelve percent of TAC treatment responses could not be determined from the provided data. All 24 patients with a

**Table 1. Baseline characteristics, pretreatment and treatment details, and treatment outcomes of the Dutch case series**

| | Cyclosporine (*n*=1) | Tacrolimus (*n*=8) | |
|---|---|---|---|
| | First-line treatment intolerance (*n*=1) | First-line treatment intolerance (*n*=3) | First-line treatment insufficient response (*n*=5) |
| Baseline characteristics | | | |
| Sex (male/female) | 0/1 | 0/3 | 3/2 |
| Age at diagnosis (years) | 20 | 56 (36–65) | 28 (26–63) |
| Disease duration (years) | 8 | 7 (2–12) | 8 (2–16) |
| IgG/gamma globulin elevated at diagnosis | 1 | 2/2 (100%) | 3/4 (75%) |
| ANA | 1 | 2/3 (67%) | 3/5 (60%) |
| ASMA | 1 | 3/3 (100%) | 4/5 (80%) |
| SLA | 0 | 1/1 (100%) | 0/2 (0%) |
| LKM | 0 | 0/2 (0%) | 0/3 (0%) |
| AMA | 0 | 0/3 (0%) | 0/4 (0%) |
| Liver biopsy at diagnosis | 1 | 3/3 (100%) | 5/5 (100%) |
| Interface hepatitis | 1 | 2/3 (67%) | 5/5 (100%) |
| Plasma cell infiltrate | 1 | 2/3 (67%) | 5/5 (100%) |
| Biliary changes | 1 | 1/3 (33%) | 3/4 (75%) |
| Cirrhosis at diagnosis | 0 | 0/3 (0%) | 1/5 (20%) |
| Pretreatment details | | | |
| Max AZA dosage (mg/day) | 50 | 100 (75–100) | 100 (50–200) |
| PRED/Budesonide (*N*)[†] | 1/0 | 2/2 | 5/4 |
| Pretreatment duration (months) | 1 | 2 (1–5) | 18 (4–184) |
| Second-line treatment before CNI, reason for start CNI | No | 1 MMF, insufficient response; 1 MMF, intolerance | No |
| CNI treatment details | | | |
| Treatment duration (months) | 94 | 8 (1–34) | 27 (14–60) |
| Maximum dose | 4.5 (mg/kg/day) | 4 (1–5) (mg/day) | 4.5 (3–8) (mg/day) |
| Through level (ng/mL) | 100–400 | 4–15 | 4–15 |
| Co-medication[†] | PRED, BUD | 2 PRED; 1 PRED, BUD | 3 PRED; 2 PRED, BUD |
| Stopped | 0 | 2 | 2 |
| Result of CNI treatment | | | |
| Remission | 0 | 0 | 1 (20%) |
| Response | 0 | 0 | 4 (80%) |
| Treatment failure | 1 | 3 (100%) | 0 |
| Long-term outcome of CNI treatment | | | |
| Remission/response CNI | 0 | 0 | 5 (100%) |
| Stable disease[‡] | 1 | 2 | 0 |
| Progression, decompensated cirrhosis | 0 | 1 | 0 |
| Follow-up (months) | 98 | 26 (8–34) | 27 (14–60) |

Median (range), number positive/number measured or known (%). [†]Multiple patients were treated with PRED and consecutively with BUD; [‡]No disease progression compared with baseline situation, and without remission or response. AZA, azathioprine; BUD, budesonide; CNI calcineurin inhibitor; MMF, mycophenolate mofetil.

**Table 2. Systematic review of cyclosporine in adult AIH patients: data on treatment before starting cyclosporine**

| Study | | N | Age min-max (year) | Pretreatment | Treatment duration before start CNI min-max (months) | Reason for starting CNI |
|---|---|---|---|---|---|---|
| Mistilis | 1985 | 1 | 51 | PRED/AZA | 59 | Intolerance |
| Person | 1993 | 1 | 31 | PRED/AZA | 15 | Insufficient response |
| Sherman | 1994 | 4 | 27–52 | 4 PRED/AZA | 6–36 | 4 Insufficient responses |
| Lawrence | 1994 | 1 | 39 | PRED/AZA | 25 | Insufficient response |
| Senturk | 1995 | 1 | 33 | PRED/AZA | 8 | Insufficient response |
| Fernandes | 1999 | 5 | 19–62 | 2 PRED; 3 PRED/AZA | 3–12 | 5 Insufficient responses |
| Malekzadeh[†] | 2001 | 10 | 16–44 | 7 PRED; 3 PRED/AZA | ? | 5 Insufficient responses; 5 Intolerance |
| Wah-Kheong | 2012 | 1 | 50 | PRED/AZA | 23 | Intolerance |
| Pape[†‡] | 2019 | 9 | 19–66 | 3 PRED/AZA; 5 PRED/AZA, MMF; 1 PRED/AZA, 6-MP | ? | 5 Insufficient responses; 4 Intolerance |
| Noguchi | 2020 | 8 | 30–55 | 2 PRED; 6 mPRED | 1–3 | 8 Insufficient responses |
| Roberts[†] | 2020 | 17 | 35 (median) | 15 PRED/AZA; 1 PRED/6-MP; 1 PRED; 3 MMF | ? | 12 Insufficient responses; 5 Intolerance |
| Dutch cohort | | 1 | 20 | 1 PRED/AZA | 1 | 1 Intolerance |
| | | | | | | |
| Summary | | 59 | 16–66 | 50 CYC as second-line treatment; 9 CYC as third-line treatment | | 42 Insufficient responses; 17 Intolerance |

[†]Portion of the entire case series. [‡]Treatment duration not reported for cyclosporine patients only. 6-MP, 6-mercaptopurine; AZA, azathioprine; CYC, cyclosporine; MMF, mycophenolate mofetil; mPRED, methylprednisolone; PRED, prednisolone.

known time to remission reached remission within 12 months after initiation of TAC. Treatment with TAC was discontinued in 39 patients (18%). The reasons for discontinuing TAC were intolerable adverse effects in 24 patients (11%), an insufficient response to TAC treatment in nine (4%), persistent remission in two (1%), because of an adjustment of the diagnosis (from AIH to AIH-PSC variant syndrome) in two (1%), and TAC was stopped on the patient's own initiative in two (1%).

### *Tacrolimus: adverse effects*

In most studies, adverse effects were reported collectively, not per patient, and multiple adverse effects could occur in one patient. Some studies only reported major events or reasons for stopping TAC treatment. Supplementary Figure 2 shows the minimal number of patients per side effect reported. Twenty four of the 219 patients (11%) stopped using TAC because of intolerable adverse effects, five patients with gastrointestinal adverse effects (diarrhea,/abdominal pain or unspecified), five with neurological adverse effects (unspecified), three with hypertension and/or tremor and/or edema, two with renal failure, two with gastrointestinal hemorrhage, one with headache and vomiting, one with headache and tremor, one with hair loss, one with hemolytic uremic syndrome, one with a squamous cell carcinoma. The reason was not specified in two patients.

### *Insufficient response versus intolerance to first-line treatment*

A total of 200 patients were treated with a CNI because of an insufficient response to first-line treatment (Tables 2 and 4). Remission was reached in 105 patients (53%), 37 (19%) had a response without remission and 13 (7%) had treatment failure on CNI. In 45 patients (22%), the result of CNI treatment could not be linked to the reason for starting a CNI or could not be determined from the provided data (Fig. 2). A total of 60 patients were treated with a CNI because of intolerance to first-line treatment (Table 2 and Table 4). Remission was reached in 40 patients (67%), one patient (2%) had a response without remission, and 6 (10%) had treatment failure on CNI. In 13 patients (22%) result of CNI treatment could not be linked to the reason for starting a CNI or could not be determined from the provided data (Fig. 2). There were no significant differences in remission rate, response rate, treatment failure (chi-square for trend, $p$=0.498), treatment duration (median 22.5 vs. 29 months, $p$=0.934) or follow-up (median 24 vs. 25 months, $p$=0.726) between patients treated with CNI because of insufficient response to first-line treatment and because of intolerance to first-line treatment (Fig. 2).

### *Second versus third-line treatment*

A total of 203 patients (73%) received CNIs as second-line treatment (Tables 2 and 4). Remission was reached in 106 patients (52%), 20 (10%) had a response and 20 (10%) had treatment failure. In 57 patients (28%), the result of CNI treatment could not be linked to the line of treatment or could not be determined from the provided data (Fig. 2). A total of 62 patients (22%) received CNIs as third-line treatment (Tables 2 and 4). Remission was reached in 16 patients (26%), 10 (16%) had a response, and four (6%)

**Table 3. Systematic review of cyclosporine in adult AIH patients: data on cyclosporine treatment**

| Study | | n | Age min-max (year) | Start dosage min-max (mg/kg/day) | Through level min-max (ng/mL) | Co-medication | Treatment duration min-max (months) | Adverse effects | Result of treatment | Follow-up min-max (months) |
|---|---|---|---|---|---|---|---|---|---|---|
| Mistilis | 1985 | 1 | 51 | 3 | No | PRED | 24 | Rise in Creatinine | Response | 24 |
| Person | 1993 | 1 | 31 | ? | 80–130 | PRED/AZA | 21 | No | Remission | 39 |
| Sherman | 1994 | 4 | 27–52 | 3 | 180–220 | 1 No; 3 PRED/AZA | 4–26 | 4 Gingival hyperplasia; 1 Paresthesia; 1 Rise in creatinine | 2 Remission; 1 Response; 1 Treatment failure | 4–26 |
| Lawrence | 1994 | 1 | 39 | 2.5 | 200 | No | 9 | No | Response | 9 |
| Senturk | 1995 | 1 | 33 | 3 | 100–300 | No | 15 | 1 Rise in creatinine | Remission | 15 |
| Fernandes | 1999 | 5 | 19–62 | 2–5 | No | 2 No; 3 PRED | 12–63 | 2 Hypertrichosis; 2 Gingival hyperplasia; 1 Varicella zoster | 4 Remission; 1 Response | 12–63 |
| Malekzadeh[†] | 2001 | 10 | 16–44 | 2–5 | 100–300 | ? | ?–6 | Yes[‡] | 4 Remission; 5 Response; 1 Treatment failure | Unknown |
| Wah-Kheong | 2012 | 1 | 50 | ? | No | PRED | 9 | No | Remission | 9 |
| Pape[†§] | 2019 | 9 | 19–66 | 1.2–3.8 | ? | 3 No; 4 PRED; 1 AZA; 1 BUD | ? | Headache; Flu-like symptoms; Gingival hyperplasia | 4 Remission; 1 Treatment failure; 4? | ? |
| Noguchi | 2020 | 8 | 30–55 | 2–5 | 150–200 | 2 PRED; 6 mPRED | 1–17 | 3 Tremor; 1 Rise in creatinine; 1 Thrombo-cytopenia; 1 CMV reactivation | 8 Remission | 7–118 |
| Roberts[†] | 2020 | 17 | 35 (median) | 120 (median, mg/day) | No | ? | 240 (median) | 4 Rise in creatinine; 4 Gingival hyperplasia; 3 Skin disorders; 3 Infection; 2 Hypertension; 1 Neurological[¶] | 10 Remission; 4 Response; 3 Treatment failure | 308 (median) |
| Dutch cohort | | 1 | 20 | 4.5 | 100–400 | PRED | 94 | No | 1 Treatment failure | 98 |
| Summary | | 59 | 16–66 | | | 8 No; 12 PRED; 6 mPRED; 4 PRED/AZA; 1 AZA; 1 BUD; 27? | | | 35 Remission; 13 Response; 7 Treatment failure; 4? | |

[†]Portion of the entire case series; [‡]Frequencies of side effects only reported for the entire case series; [§]Treatment duration and follow-up not reported for cyclosporine patients only; [¶]Included tremor, paresthesia, headache, migraine, anxiety. AZA, azathioprine, BUD, budesonide; CYC, cyclosporine; mPRED, methylprednisolone; PRED, prednisolone.

**Table 4. Systematic review of tacrolimus in adult AIH patients: data on treatment before starting tacrolimus**

| Study | | n | Age min-max (year) | Pretreatment | Treatment duration before start CNI min-max (months) | Reason for starting CNI |
|---|---|---|---|---|---|---|
| Aqel | 2004 | 11 | 44–84 | 10 PRED/AZA, 1 PRED | 6–14 | 11 Insufficient responses |
| Chatur† | 2005 | 5 | Adult | 5 PRED? AZA | ? | Not specified |
| Larsen | 2007 | 9 | 16–64 | 6 PRED/AZA, 3 PRED/MMF | 3 | 9 Insufficient responses |
| Tannous | 2011 | 13 | 40.6 (mean) | ? | ? | Not specified |
| Than | 2016 | 17 | 16–70 | 5 PRED/AZA, 3 PRED/AZA, CYC, 3 PRED/AZA, MMF, 1 PRED, 1 BUD, 1 AZA, 1 PRED/AZA, 6-MP, CYC, 1 PRED/AZA, 6-MP, MMF, CYC, 1 PRED/AZA, 6-MP, MMF | ? | 16 Insufficient responses; 1 Intolerance |
| Rubin† | 2016 | 1 | 61 | 1 PRED/AZA, MMF | 42 | 1 Insufficient response |
| Al Taii | 2017 | 23 | 15–49 | 23 PRED, 19 AZA, 10 MMF, 9 BUD | ? | 23 Insufficient responses |
| Efe† | 2017 | 87 | 10–67 | 80 AZA, PRED, or BUD; 7 AZA, PRED or BUD, MMF | 3–182 | 53 Insufficient responses; 34 Intolerance |
| Pape†§ | 2019 | 6 | 21–57 | 2 PRED/AZA, 2 PRED/AZA, MMF, 1 PRED/6-TG, MMF; 1 PRED/AZA, 6-TG | ? | 5 Insufficient responses; 1 Intolerance |
| Ferre-Aracil | 2020 | 23 | 48‡ | 20 PRED, 3 BUD, 22 Thiopurine, 5 MMF, 1 CYC | Median 24, IQR 84 | 20 Insufficient responses; 3 Intolerance |
| Roberts† | 2020 | 16 | 17 (median) | 15 AZA, PRED, or BUD; 1 6-MP, PRED or BUD; 11 MMF | ? | 15 Insufficient responses; 1 Intolerance |
| Dutch cohort | | 8 | 26–65 | 1 BUD/AZA, MMF, 1 PRED/AZA, MMF, 1 PRED/AZA, 5 PRED/AZA, BUD | 1–184 | 5 Insufficient responses; 3 Intolerance |
| Summary | | 219 | 10–84 | 153 TAC as second-line treatment; 53 TAC as third-line treatment; 13? | 1–184 | 158 Insufficient responses; 43 Intolerance; 18 Not specified |

†Portion of the entire case series; §Treatment duration not reported for tacrolimus patients only. 6-MP, 6-mercaptopurine; 6-TG, 6-thioguanine; AZA, azathioprine; BUD, budesonide; CYC, cyclosporine; MMF, mycophenolate mofetil; PRED, prednisolone; UDCA, ursodeoxycholic acid.

had treatment failure. In 32 patients (52%) the result of CNI treatment could not be linked to the line of treatment or could not be determined from the provided data (Fig. 2).

There was no significant difference in the numbers of patients receiving CYC as second- ($n$=50, 85%) or third-line ($n$=9, 15%) treatment compared with the number of patients receiving TAC as second- ($n$=153, 74%) or third-line ($n$=53, 26%) treatment ($p$=0.116). Patients receiving CNI as second-line treatment had a significantly higher remission rate compared with patients receiving CNI as third-line treatment. In patients receiving CNI as third-line treatment the outcome was significantly more often unknown compared with the outcomes of patients receiving CNI as second-line treatment (chi-square for trend, $p$<0.001; Fig. 2).

## Discussion

This systematic review of the literature, with the addition of a novel Dutch case series, summarizes and evaluates the use of CNIs in the treatment of over 250 difficult-to-treat adult AIH patients over the last decades. Although several systematic reviews were published on CNIs in the treatment of adult AIH, interpretation of the published data is hampered by heterogeneity of the outcome measures.[16–21] In this systematic review, we addressed that problem by redefining the treatment outcomes in the articles according to established definitions.[16–20] In studies describing the use of MMF in the treatment of AIH, the reason for starting MMF (e.g. intolerance or insufficient response to first-line treatment) appeared to be an important factor.[5,45,46] A recently published position statement also emphasized the importance of the reason for changing treatment.[47] Importantly, in this current systematic review there was no difference in response to CNI treatment in patients with intolerance to treatment versus patients with insufficient response to first-line treatment.

The efficacy of both CYC and TAC in the treatment of adult AIH patients seems fairly good, with remissions rates of 59% for both CYC and TAC. If reported, most remissions were achieved within the first year of treatment, which is prognostically favorable.[25] CNI monotherapy was used in a minority, 14% in CYC patients and 11% on TAC, while most patients were treated in combination with corticosteroids and/or another immunosuppressants (Tables 3 and 5). In patients using CNIs because of insufficient response to first-line treatment, the remission rate was 53% (Fig. 2). Two previously published reviews reported pooled remission rates of 41% and 32% on MMF.[21,48] Compared with MMF, CNIs seem more effective in that group, but there is no available head-to-head comparison.

In patients using CNIs for intolerance to first-line treatment remission rate was 67% (Fig. 2), which seems less effective compared to MMF with pooled remission rates in first-line intolerant patients of 74% and 82%.[21,48] As the

**Table 5. Systematic review of tacrolimus in adult AIH patients: data on tacrolimus treatment**

| Study | | n | Age min-max (year) | Start dosage min-max (mg/day) | Through level min-max (ng/mL) | Co-medication | Treatment duration min-max (months) | Adverse effects | Result of treatment | Follow-up min-max (months) |
|---|---|---|---|---|---|---|---|---|---|---|
| Aqel | 2004 | 11 | 44–84 | 1 | <6 | 9 PRED/AZA; 1 PRED; 1 PRED/Sirolimus | 1–36 | 4 Headache; 1 Hypertension; 1 Tremor; 1 Generalized edema; 1 Vivid dreams | 9 Remission; 2 Treatment failure | ?–36 |
| Chatur[†] | 2005 | 5 | Adult | 1–4 | No | 3 PRED; 2 PRED/MMF | 6–? | 1 Abdominal pain; 1 Tremor | 1 Remission; 3 Response; 1 Treatment failure | 10–54 |
| Larsen | 2007 | 9 | 16–64 | 2–4 | <6 | 6 PRED/AZA; 3 PRED/MMF | 12–37 | 1 Tremor | 3 Remission; 6 Response | 12–37 |
| Tannous | 2011 | 13 | 40.6[‡] | 2–6 | ? | ? | 1–65 | 1 Nausea and vomiting; 1 Hair loss; 1 HUS; 1 SSC | 11 Remission; 2 Treatment failure | 1–65 |
| Than | 2015 | 17 | 16–70 | 0.5–5 | <6 | 6 PRED; 5 PRED/AZA; 2 AZA; 2 BUD/MMF; 1 BUD/AZA; 1 PRED/MMF | 12–136 | 2 Headache; 1 Tremor; 1 Psychosis; 1 Abdominal pain; 1 Nausea and vomiting | 5 Remission; 3 Treatment failure; 9? | 12–204 |
| Rubin[†] | 2016 | 1 | 61 | 5 | No | 1 PRED/MMF | 12 | 1 Renal failure | 1 Treatment failure | 39–147 |
| Al Taii | 2017 | 23 | 15–49 | 5 (mean) | ? | ? | 35 (median) | 2 Gastrointestinal hemorrhage* | 6 Remission; 10 Response; 7 Treatment failure | ? |
| Efe[†] | 2017 | 87 | 10–67 | 1–8 | No | 20 No; 8 MMF; 59? | ? | 4 Neurologic; 2 Hypertension and generalized edema; 2 Gastrointestinal; 1 Hair loss; 1 Renal failure | 65 Remission; 10 Treatment failure; 12? | 7–190 |
| Pape[†¶] | 2019 | 6 | 21–57 | 1–5 | ? | 1 No; 5 PRED | ? | 3 Tremor; 2 Nausea; 1 Diarrhea; 1 Vertigo | 5 Remission; 1? | ? |
| Ferre-Aracil | 2020 | 23 | 48[‡] | ? | ? | 2 No; 16 Steroids; 6 MMF; 6 Thiopurine | 16 (median, IQR 20) | 3 Tremor; 2 Headache; 1 Diabetes; 1 Hypertension; 1 Diarrhea; 1 Neuropathy and ototoxicity | 18 Remission; 1 Treatment failure; 4? | 3–242 |
| Roberts | 2020 | 16 | 17 (median) | 2.0 (median) | No | ? | 102 (median) | 9 Neurological[#]; 3 Fatigue; 2 Infection; 2 Rise in creatinine; 2 Skin disorders; 1 Hyperkalemia | 6 Remission; 10 Response | 102 (median) |

*(continued)*

**Table 5.** *(continued)*

| Study | n | Age min-max (year) | Start dosage min-max (mg/day) | Through level min-max (ng/mL) | Co-medication | Treatment duration min-max (months) | Adverse effects | Result of treatment | Follow-up min-max (months) |
|---|---|---|---|---|---|---|---|---|---|
| Dutch cohort | 8 | 26–65 | 1–8 | 4–15 | 5 PRED; 3 PRED → BUD | 1–60 | 3 Tremor; 3 Headache; 1 Abdominal pain; 1 Nausea; 1 Diarrhea; 1 Insomnia | 1 Remission; 4 Response; 3 Treatment failure | 8–60 |
| Summary | 219 | 10–84 | 1–8 | 4–15 | 23 No; 20 PRED/AZA; 20 PRED; 8 MMF; 7 PRED/MMF; 3 PRED → BUD; 2 AZA; 2 MMF/BUD; 1 AZA/BUD; 1 PRED /Sirolimus; 95? | 1–136 | | 130 Remission; 33 Response; 30 Treatment failure; 26? | 1–204 |

†Portion of the entire case series; ‡Mean; §Frequencies of side effects only reported for the entire case series; ¶Treatment duration and follow-up not reported for tacrolimus patients only; #Included tremor, paresthesia, headache, migraine, anxiety; *Gastrointestinal hemorrhage most likely was a complication of cirrhosis and not related to the drug. AZA, azathioprine; BUD, budesonide; HUS, hemolytic uremic syndrome; MMF, mycophenolate mofetil; PRED, prednisolone; SCC, squamous cell carcinoma; TAC, tacrolimus.

adverse effect profile of MMF is also more favorable than that of TAC,[49] it seems rational to use MMF as second-line treatment in patients with intolerance to first-line treatment, although TAC can certainly be considered in such patients. CNIs were predominately used as second-line treatment, which seemed to be more effective than as third-line treatment, but interpretation is hampered by the fact that data on treatment outcome was more often missing in the third-line treatment group.

Figure 3 summarizes the options after first-line treatment failure. Despite this, a small number of patients will fail CNI treatment because of intolerance (13 % CYC and 11% TAC) or failure to achieve or maintain remission. If treatment failure occurs when CNIs were used as second-line treatment, MMF is the most logical next option, regardless of the reason (intolerance or insufficient response) for switching to CNIs. MMF is the most investigated alternative. As discussed above, it achieves reasonable remission rates, and it is the most used second-line treatment in a real world analysis.[9,21,48] If treatment failure occurs when CNIs are used as third-line treatment, and unless MMF has not already been used, patients depend on salvage therapies like methotrexate, infliximab, rituximab, sirolimus, and everolimus.[10–14] It is recommended to send patients to specialized centers for second and third-line or salvage treatment.

There is extensive experience and safety data with the use of CNIs in liver and other organ transplantation. Of the CNIs, TAC currently is the drug of choice in almost 90% of liver transplantations because of easier drug monitoring, better long-term graft and patient survival with less rejection compared to CYC, and the availability of a once-daily prolonged-release formula, which has a positive impact on patient adherence.[50] Currently, most treating physicians probably prefer TAC over CYC if a CNI is needed in AIH, but there are no published head-to-head comparisons in AIH patients.

### *Safety*

Overall, CNI treatment seems to be well tolerated in adult AIH patients. Thirteen percent stopped using CYC and 11% stopped using TAC because of intolerable adverse effects, including only three patients because of renal problems. Minor adverse effects were more prevalent, but can often be controlled by adjustment of the dosage. One reason why CNIs were so well tolerated may be the relatively low through levels maintained compared with the levels obtained in solid organ, including liver, transplantation. Most studies of the use of TAC mainly aimed for through levels of < 6 ng/mL. In the Dutch cohort, the target through levels were below 6 ng/mL in five of the eight patients. The target levels were higher in three patients, but were still below 15 ng/mL. One of the three patients had dose-related adverse effects that were controlled by lowering the dose. Therefore, initially aiming at a TAC trough level of 3–7 ng/mL seems reasonable, especially if combined with other immunosuppression.

### *Limitations*

Despite the more granular data compared with other reviews on the subject, this systematic review, including a novel Dutch case series, has some limitations. The very low rating of the data per outcome according to the GRADE approach (Supplementary Table 1) introduces a high risk of publication and selection bias. All the selected studies were case reports or case series. There is only one case report with treatment failure as a result of CNI treatment, pos-

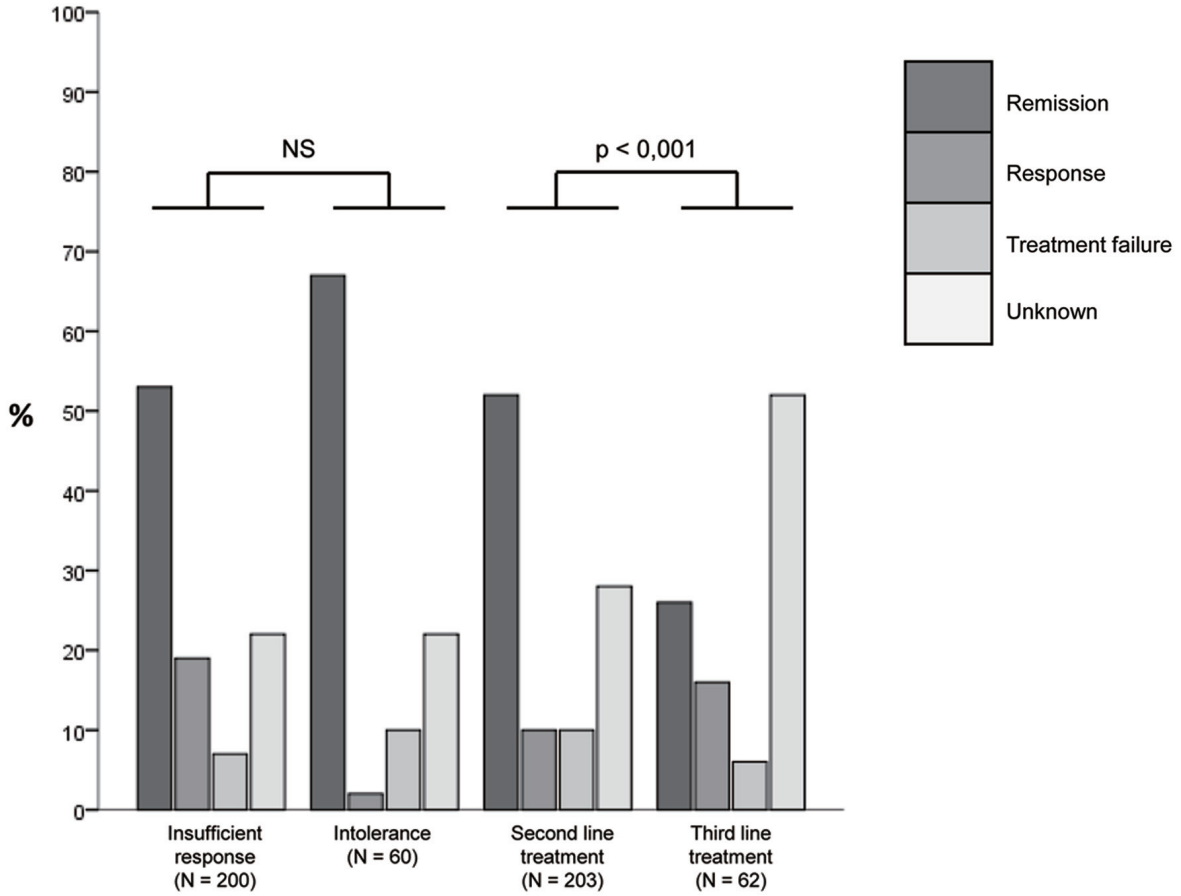


**Fig. 2. Results of calcineurin inhibitor treatment.** Insufficient response versus intolerance, and second-line versus third-line treatment.

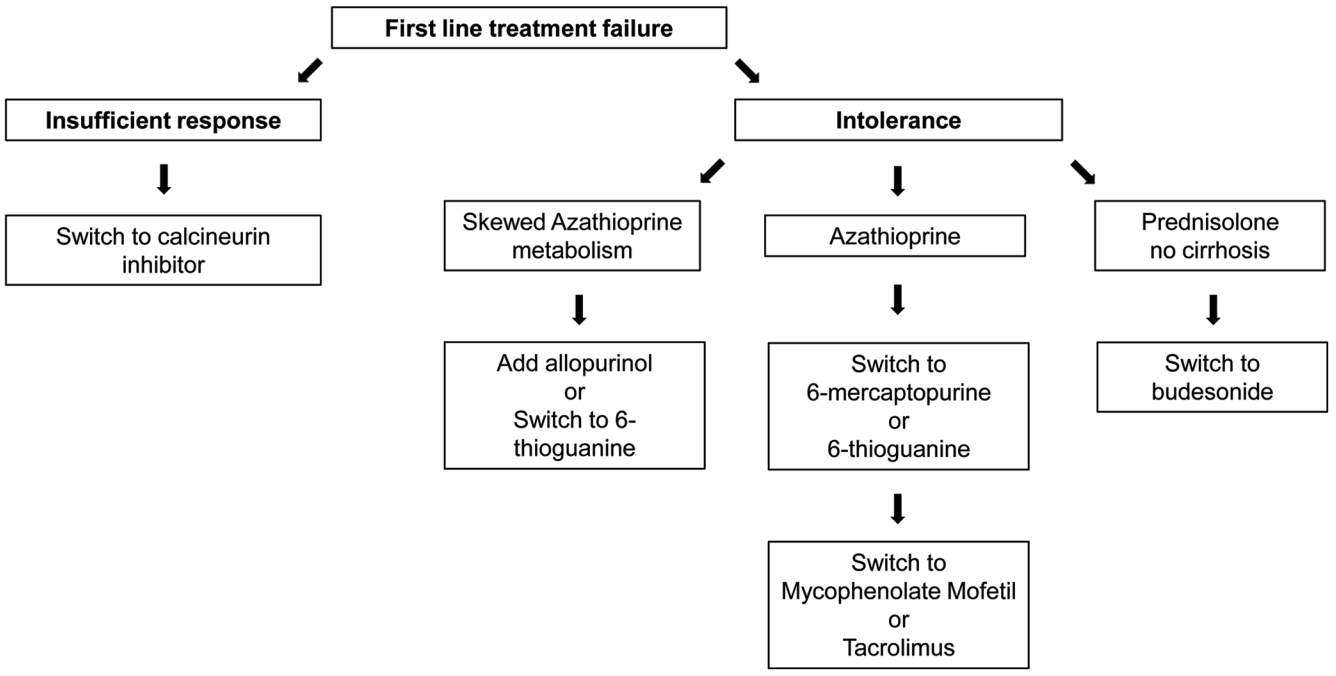


**Fig. 3. Treatment options after first-line treatment failure.**

sibly reflecting underreporting of such cases. Most publications reported the results of retrospective studies, resulting in heterogeneity and missing data. Baseline characteristics and treatment outcome were often reported independently, making it impossible to analyze the influence of patient characteristics, such as cirrhosis or sex, on treatment outcome and follow-up was often short. Despite the limitations, conclusions could be drawn from the combined data that may be important for guiding the choices that need to be made in difficult-to-treat AIH. The data may also be the basis for future prospective studies that are currently being planned.

## Conclusions

Despite the limitations mentioned and bearing in mind that the quality of the evidence is low, it can be concluded that:

- CNIs appear effective in patients failing first-line treatment, with remission rates of 59% for CYC and TAC.
- CNIs seem to be more effective than MMF in patients with an insufficient response to first-line treatment, with remission rates of 53%.
- CNIs seem to be less effective than MMF in patients intolerant to first-line treatment, but is has a remission rate of 67%.
- CNIs seemed to be more effective as second-line treatment than as third-line treatment. Interpretation was hampered by missing data and selection bias.
- CNI treatment in adult AIH appeared to be well tolerated.

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## Conflict of interest

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## Author contributions

Study conceptualization and design (MAMC Baven-Pronk, JM Hew Jr, B van Hoek), study supervision (B van Hoek), data collection and provision (JM Hew Jr, M Biewenga, ME Tushuizen, AP van der Berg, G Bouma, JT Brouwer), data analysis and interpretation (MAMC Baven-Pronk, JM Hew Jr), statistical analysis (MAMC Baven-Pronk), manuscript drafting (MAMC Baven-Pronk, JM Hew Jr), manuscript critical revision for important intellectual content (M Biewenga, ME Tushuizen, AP van der Berg, G Bouma, JT Brouwer, B van Hoek), final draft approval (MAMC Baven-Pronk, JM Hw Jr, M Biewenga, ME Tushuizen, AP van der Berg, G Bouma, JT Brouwer, B van Hoek).

## Data sharing statement

The data for this study are available from the corresponding author upon reasonable request.

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