The Use of Cyclosporine A in Rheumatology: A 2016 Comprehensive Review

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Abstract

Cyclosporine A, an inhibitor of calcineurin, exerts an immunomodulator action interfering with T cell activation. Even though novel therapeutic tools have emerged, CyA still represents a suitable option in several clinical rheumatology settings. This is the case of refractory nephritis and cytopenias associated with systemic lupus erythematosus. Furthermore, CyA is a valued therapeutic tool in the management of uveitis and thrombophlebitis in course of Behçet's disease. Topical CyA has been proven to be beneficial in the dry eye of Sjogren's syndrome, whereas oral treatment with CyA can be considered for the severe complications of adult onset Still's disease. CyA provides a therapeutic option in psoriatic arthritis, being rather effective in skin disease. CyA is currently regarded as a second-line option for patients with inflammatory myopathies refractory to standard regimen. CyA is used even in paediatric rheumatology, in particular in the management of juvenile dermatomyositis and macrophage activation syndrome associated with systemic juvenile idiopathic arthritis. Importantly, CyA has been shown to suppress the replication of HCV, and it can thus be safely prescribed to those patients with chronic hepatitis C. Noteworthy, CyA can be administered throughout the gestation course. Surely caution should be paid to CyA safety profile, in particular to its nephrotoxicity. Even though most evidence comes from small and uncontrolled studies with few randomized controlled trials, CyA should be still regarded as a valid therapeutic tool in 2016 rheumatology.

Key words

1. Cyclosporine
2. Rheumatology
3. Arthritides
4. Connective tissue diseases
5. Vasculitides
6. Hepatitis C virus

Introduction

The earliest use of cyclosporine (CyA) in the field of rheumatology dates back to 1979, when the first trial in patients with inflammatory arthritides was conducted [1]. Since then, CyA has been used to manage several autoimmune conditions: thanks to its mechanism of action, this pharmacological compound is potentially effective in different clinical settings.

Mechanism of action of cyclosporine A

Initially developed as an anti-mycotic agent, CyA is an 11-aminoacid peptide originally isolated from a soil fungus. Its immunosuppressive properties have been described in the 70s, when it was first employed as an anti-rejection agent for organ transplantation. CyA is a pro-drug, which becomes active after complexing with cyclophillin, an intra-cytoplasmatic protein. The CyA-cyclophillin complex in turn inhibits calcineurin, a phosphatase that mediates the pharmacological effects of CyA. Indeed, calcineurin induces the translocation into the nucleus of the nuclear factor of activated T cells (NF-AT), which acts as transcription factor for a number of pro-inflammatory cytokines, such as interleukin (IL)-2, IL-2 receptor, IL-4, interferon (IFN)-γ and transforming growth factor–β (TGF-β). The inhibition of IL-2 and IL-2 receptor, the two main stimulating pathways involved in T cell activation, accounts for the action of CyA on T cells: it impairs the activation of T helper (Th) cells, even though the T suppressor (Ts) subset may also be affected [2]. The pharmacological action of CyA is schematically presented in **Figure 1**.

Pharmacokinetics of cyclosporine A

Two formulations of CyA have been developed: the original one (Sandimmune) displays a poor bioavailability and larger inter and intra-subject pharmacokinetic variability; the most recent microemulsion (Neoral) offers a better bioavailability and a more predictable pharmacokinetics and dose linearity. Because of its lipophilic nature, plasma CyA is almost exclusively bound to lipoproteins, explaining why CyA serum concentrations might be affected by dietary fat intake.

Indeed, raised serum lipid levels can increase CyA total body clearance: a higher serum CyA concentration results when the drug is administered before rather than after meals, accounting for higher clinical efficacy [2].

CyA displays a first-pass effect of 27% in the liver; the enterohepatic recirculation of CyA from the bile to the small intestine is responsible of its biphasic distribution. CyA half-life in serum ranges between 6 and 24 hours; its oral bioavailability and systemic clearance are controlled by the cytochrome P450 and the efflux p-glycoprotein pump, a trans-membrane transporter expressed in the gastrointestinal tract and in the liver. CyA metabolites are excreted primarily in the bile, with only 6% of the dose being excreted in the urine [2].

Cyclosporine A in rheumatoid arthritis

The rationale of CyA use in rheumatoid arthritis (RA) is supported by its mechanism of action: besides the inhibition of T cells, CyA has been demonstrated to suppress IL-17 production *in vitro*. This results in the impairment of the differentiation of Th17 cells, a distinct lineage of pro-inflammatory Th cells regarded as key effectors in RA pathogenesis [3]. The 2008 updated guidelines issued by the American College of Rheumatology (ACR) do not enlist CyA as a therapeutic option in the management of RA [4]. As a matter of facts, evidences about CyA efficacy in RA are not recent, and not so solid to support its routine use (**Table 1**). Over the years, CyA has been proven to be more effective than placebo in disease control [5-9], even at long term [10], delaying radiological progression [11-13]. Controlled trials have shown CyA to be as effective as parenteral gold [14,15], D-penicillamine [16], hydroxychloroquine (HCQ) and azathioprine (AZA) [17-19], but less effective than methotrexate (MTX) [20-22].

Combining CyA with HCQ, chloroquine or gold has been observed to convey no clear benefit [23-26]. Conversely, association regimens comprising CyA plus MTX have been demonstrated to allow a greater rate of disease control as compared to CyA monotherapy [27-30] and CyA plus leflunomide (LEF) [31], using a step-up or a step-down approach. Clinical studies have investigated

the combination regimen of CyA plus MTX to MTX alone, reporting a greater beneficial effect for the combo approach [32-34], a benefit not sustained on the long-term [35]. Consistently, MTX non responder patients have been shown to present a better disease course when randomized to MTX plus CyA than when receiving MTX plus placebo [36,37]. On the other hand, the addition of CyA to MTX and infliximab (IFX) has been proven to result only in a modest increase in the response [38,39], even though CyA plus MTX association regimen has been shown to be effective in maintaining disease remission after suspension of treatment with tumour necrosis factor (TNF) inhibitors in 62% of patients [40], avoiding even erosive progression at MRI [41]. A 2001 meta-analysis of randomized controlled trials (RCT) evaluating the optimal step-up strategy in patients with an incomplete response to MTX has found that the addition of CyA, etanercept (ETN), IFX or LEF results in a comparable ACR20 response at 24-30 weeks of combination therapy [42].

Cyclosporine A in psoriatic arthritis

CyA has been shown to be more effective in the management of psoriatic arthritis (PsA) as compared to RA [43]. Such observation might be explained by the pivotal role played by IL-17 axis in PsA pathogenesis. Furthermore, CyA inhibits vascular endothelial growth factor (VEGF), a key mediator of the angiogenesis characteristic of PsA rather than RA synovium [44,45]. In the 2008 treatment guidelines for PsA, CyA is recommended in the management of moderate or severe peripheral arthritis, moderate to severe skin and nail disease [46]. Clinical improvement becomes usually evident after 3-4 weeks of treatment with CyA; response of both skin and joint involvement is dose-related, with the lowest optimal effective maintenance dose being around 3 mg/Kg.

Observational studies have shown CyA to exert a beneficial effect in reducing peripheral (but not axial) joint involvement in patients with PsA [47-50]. Controlled trials have reported that CyA is as effective as MTX, but with a higher withdrawal rate [51], and more effective than sulfasalazine (SSZ) [52]. The association of CyA with MTX has been shown to lead to a significantly better joint disease control than MTX alone [53]; the addition of CyA to ETN in patients with PsA and

uncontrolled cutaneous disease has emerged to be a safe and effective therapeutic option [54], being even better on psoriatic skin involvement than ETN plus MTX [55]. Response to CyA in PsA has been found to be persistent at two-year follow-up [56], controlling also the radiological damage [57]. Clinical studies on CyA in PsA are detailed in **Table 2**.

Cyclosporine A in systemic lupus erythematosus

In vivo, treatment with CyA has been found to prolong the life span of NZB/W F1 mice, reducing anti-DNA antibody titers [58-60]. The earliest experience with CyA treatment in patients with systemic lupus erythematosus (SLE) dates back to 1981; nowadays, CyA is not so commonly prescribed to lupus patients. In several small observational studies, CyA, alone or in combination with other agents, has been shown to reduce disease activity and improve immunological parameters such as anti-dsDNA titers and complement levels, allowing steroid tapering [61-69](**Table 3**). In particular, CyA has been shown to be beneficial in some lupus manifestations, and it might be taken into account as therapeutic option in refractory lupus nephritis, skin disease and haematological involvement [70]. CyA efficacy in lupus nephritis is mediated not only by its immunosuppressive action but also its ability to stabilize the podocyte cytoskeleton by inhibiting dephosphorylation and degradation of synaptopodin, an actin-associated protein that regulates cell shape and motility and mediates podocyte foot processes. To note, synaptopodin downregulation and increased calcineurin activity are both associated with proteinuric glomerular diseases [71,72]. CyA is currently recommended in the management of lupus nephritis with persistent severe proteinuria, refractory to conventional treatment with corticosteroids and cytotoxic agents [70]. Indeed, according to still limited data, the association of CyA with corticosteroid therapy is effective in the treatment of class III, IV or V lupus nephritis. Most evidence suggests CyA efficacy in proliferative lupus nephritis, as supported by few case series [66,73-78] and uncontrolled trials [79,80]. In addition, CyA has been shown to be more beneficial than steroids alone [81] and as effective as AZA [82] and cyclophosphamide (CTX), both at short [83] and long term follow-up

[84]. As a whole, it can be stated that CyA treatment in proliferative lupus nephritis displays a cumulative rate of complete or partial remission approaching 90%, with an important anti-proteinuric effect [85]. CyA has been proven to be effective also in the management of membranous lupus nephritis, even though evidence comes from small retrospective studies [86-89] and a single RCT comparing CyA to CTX as adjunctive treatments to steroids [90]. A 2014 meta-analysis considering CyA and tacrolimus has concluded that calcineurin inhibitors might be regarded as a reasonable alternative to CTX in the induction treatment of active lupus nephritis, with an higher rate of complete remission (relative risk [RR]=1.56) and a better response/total remission ratio (RR=1.23) [91]. On the other hand, when evaluating prescription of CyA in lupus nephritis, it should be mentioned that in a cross-sectional study on 64 patients with lupus nephritis, CyA treatment has emerged as a risk factor for arterial hypertension, conveying a odds ratio of 5.3 [92].

Haematological abnormalities, if relapsing or refractory to steroids, have been shown to respond well to CyA. This is the case of lupus-associated thrombocytopenia [93,94], haemolytic anaemia [95], aplastic anaemia [96], red cell aplasia [97-99] and haemophagocytic syndrome [100]. Unfortunately, literature is still limited to case reports and small case series.

CyA exerts an evident steroid-sparing effect in cutaneous lupus. Unfortunately, skin disease has not provided a primary outcome measure in most studies in SLE; however, cutaneous manifestations have been reported to improve upon CyA treatment [65,68]. In addition, there are case reports of CyA efficacy in subacute cutaneous lupus erythematosus (LE) [101] and LE profundus [102], but not in discoid LE [103,104].

Cyclosporine A in systemic sclerosis

In vitro, CyA has been observed to inhibit the pro-fibrotic effects induced by TGF-β and IL-4 in fibroblasts, leading to a decreased synthesis of collagen [105-107]. Although there is a rationale for its use, data in support of the efficacy of CyA in systemic sclerosis (SSc) are not solid (**Table 4**).

CyA has been reported to significantly improve skin thickening in some, but not all, scleroderma patients; available evidence comes from small, short-term studies [69,108-111]. In particular, an improvement of oesophageal motor function has emerged with CyA treatment [111,112]; conversely, CyA has been described not to affect scleroderma-related internal organ involvement, in particular lung and cardiac disease [108]. There is a single report of the benefit of CyA in interstitial lung disease (ILD): one patient with diffuse scleroderma received CyA as maintenance therapy after CTX pulses, with evidences of stable disease at two-year clinical and radiological follow-up [113]. It is thus not surprising that the guidelines for scleroderma treatment published by the European League Against Rheumatism Scleroderma Trials and Research Group have not recommend CyA in SSc, highlighting the need of larger prospective studies [114]. It should be noted that CyA use in SSc is limited by its nephrotoxicity: indeed, CyA might affect renal function through a direct toxic action on the nephron or through an impairment of renal haemodynamic homeostasis. Consequently, CyA may not only worsen arterial hypertension, but also precipitate acute renal failure. In the past, CyA has even been proposed as risk factor for scleroderma renal crisis, but such association has not been confirmed in later studies [115].

Cyclosporine A in inflammatory myopathies

In the setting of inflammatory myopathies (polymyositis [PM] and dermatomyositis [DM]), CyA is currently regarded as a second-line option to be reserved to patients with disease refractory to standard regimen, which includes high-dose prednisone plus MTX or AZA.

Few trials have investigated CyA efficacy in inflammatory myopathies (**Table 5**). In a prospective controlled study, 10 DM patients receiving CyA have achieved a prompt remission; therapeutic failure occurred in 10% of cases as compared to 9% in those treated with standard regimen [116]. In addition, in a RCT on 36 patients (20 with DM, 16 with PM), CyA has been shown to be as effective as MTX [117]. In literature there are reports about CyA efficacy in managing DM-associated oesophageal involvement [118]. A growing body of evidence suggests the beneficial

effect of CyA in the management of ILD [119-123], also in cases resistant to steroid treatment [124,125] and those with an acute onset [126]. In particular, disease stabilization -or even an increase greater than 10% in forced vital capacity- has been reported in all series. CyA has also been compared to CTX in the management of PM/DM-ILD: in a cohort of 15 anti-Jo1-positive patients with lung involvement, high resolution scan of the chest at 12-month follow-up has revealed a disease worsening in 71% of patients treated with CyA as compared to 50% of those receiving CTX, with no differences in CT changes [127].

Cyclosporine A in systemic vasculitides

CyA is not enlisted as a therapeutic option in the current guidelines for the management of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides: the evidence of CyA efficacy in these clinical settings is rather scarce (**Table 6**). There are only anecdotal reports of patients with refractory granulomatosis with polyangiitis (GPA, formerly known as Wegener granulomatosis) successfully treated with CyA. In particular, CyA has led to the improvement of renal function and to the complete resolution of lung lesions [128-130], while in other cases CyA has not been effective in achieving disease remission [131]. A single report of CyA in eosinophilic granulomatosis with polyangiitis (EGP, formerly known as Churg-Strauss syndrome) has been published: a patient with EGP resistant to treatment with pulse intravenous CTX responded well to CyA therapy [132].

Similarly, the burden of evidence suggesting CyA efficacy in large vessels vasculitides is poor. In a RCT, CyA has been evaluated as steroid sparing agent in 22 patients with giant cells arteritis. However, the addition of CyA to corticosteroid treatment does not appear to be beneficial [133-135]. CyA has been successfully used in the management of patients with Takayasu's arteritis [134,136], in particular in those subjects with severe pyoderma gangrenosum [137,138].

Cyclosporine A in Behçet's disease

The efficacy of CyA in Behçet's Disease (BD) is supported by the inhibition of IL-1, a key-cytokine in disease pathogenesis [139]. Given the wide heterogeneity in the clinical manifestations of BD, the therapeutic approaches might be rather diverse, depending upon the presenting symptoms. Even though CyA has been shown to be effective in almost all clinical manifestations of BD, its use is currently recommended in the management of refractory ocular involvement and thrombophlebitis [140] (**Table 7**). In particular, refractory eye disease provides the main setting for CyA prescription in BD. Indeed, CyA is the agent of choice, alternatively to IFX, in the management of eye involvement not responsive to standard treatment, to be prescribed in combination with AZA and corticosteroids [140]. This recommendation is supported by three RCT concordantly showing CyA efficacy in ocular involvement [141-143], even though to a lower extent than IFX [144]. To note, CyA is rapidly effective in acute uveitis, although the beneficial effects seem to be not sustained in the long term [145,146].

CyA is currently recommended also in the management of thrombophlebitis, based on an open trial showing complete resolution of venous insufficiency with no recurrences over a two-month follow-up in seven patients [147]. In addition, CyA has been demonstrated to be effective in case of ulcers, oral as well as genital, and erythema nodosum, being superior to colchicine [143,148]. However, CyA is regarded as fourth-line agent because of its toxicity profile. In particular, because of its neurotoxicity, CyA should be not prescribed to BD patients with central nervous system involvement, unless necessary to manage intraocular inflammation [140]. CyA neurologic side effects in BD have been confirmed in three case-controlled studies [149-151].

Cyclosporine A in adult onset Still's disease

Corticosteroids still provide the mainstay of treatment of adult onset Still's disease, and MTX is the first-line steroid-sparing option. Targeted biologic agents, mainly IL-1 antagonists and TNF-α inhibitors, are reserved to refractory cases [152]. Even though there are reports of CyA efficacy as

steroid sparing agent with a rapid effect and a low recurrence rate [153], its use in adult onset Still's disease is currently limited to some of the severe manifestations of Still's disease [154]. Indeed, CyA, alone or in combination with other pharmacological tools, might be considered as an option in the management of disseminated intravascular coagulation [155,156], macrophage activation syndrome (MAS) [157,158], acquired amegakariocytic thrombocytopenia [159] and severe hepatic failure [160]. Details of studies investigating CyA in adult onset Still's disease are presented in **Table 8**.

Cyclosporine A in Sjogren's syndrome

Ex vivo studies have showed that topical CyA therapy induces a reduction in the number of activated T lymphocytes and apoptotic cells in conjunctival biopsies, a decreased expression of pro-inflammatory cytokines and a raise in goblet cell epithelial density [161-163]. Topical CyA is currently recommended in the management of dry eye (symptoms severity of level 2) associated with Sjogren's syndrome, at the dose of one drop in each eye twice daily [164]. Indeed, almost all available RCT have reported topical CyA to improve symptoms and signs of ocular sicca syndrome as compared to placebo or alternative treatment [165-169]. No clear dose-response relationship could be identified, but CyA 0.05% and 0.1% emulsions are the preparations most commonly prescribed.

Oral CyA has been evaluated in a single double-blind study conducted in a cohort of 20 patients, with a significant improvement of xerostomia and no significant differences in the Schirmer test score [170,171]. Details of studies investigating CyA in Sjogren's syndrome are presented in **Table 9**.

Cyclosporine A in paediatric rheumatology

CyA is currently used even in the field of paediatric rheumatology, with two particular indications: juvenile DM (JDM) and systemic juvenile idiopathic arthritis (sJIA). Few small retrospective

studies and case series have investigated the beneficial effects of CyA in JDM. Even though corticosteroids are the only agents currently approved by the US Food and Drug Administration for JDM, many patients require additional immunosuppressive medications. In JDM patients unresponsive to corticosteroids or immunosuppressive drugs (MTX, AZA or CTX), CyA treatment has resulted in the improvement of muscle strength, allowing steroid tapering [172-174]. None of the immunosuppressive drugs have been yet evaluated in controlled trials in children; a 5-year, phase-III, single-blind, randomized, controlled trial is currently on-going. It envisages 3 treatment arms: i) prednisone; ii) prednisone plus MTX and iii) prednisone plus CyA. This international trial involves 185 partners from 46 countries, coordinated by PRINTO (Pediatric Rheumatology International Trials Organisation) and conducted in children with newly diagnosed JDM. An analysis of primary outcome measures after 6 months of treatment has showed that time to inactive disease is significantly shorter and time to major therapeutic changes significantly longer in the combination groups compared to prednisone alone. The highest rate of adverse events has been registered in the group treated with CyA (51%) compared to MTX (28%) or prednisone alone (21%) [175].

The guidelines issued by ACR in 2013 recommends CyA as third-line treatment for sJIA children with active systemic features and a physician global assessment higher than 5 [176]. This recommendation is based upon prospective and retrospective series that have showed that CyA is effective in treatment of sJIA, leading to improvement in laboratory variables, joint counts, joint swelling, and morning stiffness in some -but not all- children, even if the improvement is not sustained at long term [173,174,177,178]. CyA has been evaluated even as second-line tool in sJIA, showing a good efficacy when associated with MTX [179]. CyA is particularly effective in MAS, a potentially life-threatening complication occurring in 7-13% of sJIA patients. Evidence of CyA efficacy in MAS associated with sJIA relies upon observational studies and case series (**Table 10**). CyA has been proven to result in clinical improvement in most patients, being particularly effective

in the management of systemic symptoms [180-187]. Importantly, CyA has been reported life-saving in serious cases of steroid resistant MAS [180].

Cyclosporine A and hepatitis C virus

CyA has been reported to suppress the replication of hepatitis C virus (HCV) both *in vitro* and *in vivo*, in a dose-dependent manner [188]. Such effect is mediated by the inhibition of cyclophillin B [189]. The maximum inhibitory effect exerted by CyA is similar to that of IFN-α; to note, these two agents are certainly additive and possibly synergistic [190]. In addition CyA displays an anti-fibrotic effect inhibiting collagen production and increasing collagenase activity in hepatic stellate cells [191]. These data account for the safety and efficacy of CyA in the treatment of patients with autoimmune disorders and concomitant chronic HCV infection, as documented by some case-series with improvement of liver function and decreased viral load [192,193]. Furthermore, CyA safety in HCV positive RA patients has been evaluated in combination with anti-TNF-α agents, without any significant adverse event [194].

Cyclosporine A and pregnancy

CyA, being highly lipophilic, crosses the placenta to achieve in the fetal circulation a 10-50% concentration of that in maternal plasma. Animal studies have not shown increased malformation rates, but *in utero* exposure to CyA in rabbits induces a nephron reduction leading to systemic hypertension and progressive chronic renal insufficiency in adulthood [195]. These *in vivo* observations explain why the FDA currently classifies CyA in the pregnancy risk category C.

Data on CyA in pregnancies are mostly derived from registries of pregnant transplant recipients, with more than 5000 observed pregnancies. Most studies of pregnancies exposed to CyA have concluded that there is no evidence for teratogenicity. On the other hand, an increase in premature delivery and low birth weight has been described, with 56% and 43% prevalence rates in a meta-analysis of 15 studies [196]. It is still not clear whether prematurity and low birth weight are

actually due to CyA therapy or rather related to the underlying disease. Conversely, experience in pregnant patients with autoimmune disease is limited to case reports and case series accounting for about 50 pregnancies. No increase of congenital malformations or any particular malformation pattern has emerged; however, a higher incidence of low birth weight and prematurity has been described in CyA-treated women with autoimmune diseases as compared to the general population, even though to a lesser extent than in transplanted women [197]. A 12-year follow-up of 175 children exposed to CyA *in utero* has showed a 16% incidence of mental developmental delay, which might be attributed to the high incidence of prematurity [198]. Other studies have shown that maternal treatment with CyA during pregnancy does not permanently affect the foetal immune system [199,200]. As a whole, CyA is considered to be safe during pregnancy, therefore treatment can be continued at the lowest effective dose throughout the entire gestation. A periodic control of maternal blood pressure and renal function should be performed on a regular basis.

Cyclosporine A and breastfeeding

CyA is excreted in breast milk, with a wide variation in the milk-to-maternal serum concentration ratio, depending on the time of sampling and maternal dose. To date, evidence on the safety of breastfeeding during CyA therapy is limited to small case series and case reports [201,202]. No adverse events related to maternal CyA treatment during lactation have been described, with CyA being undetectable in almost all cases. Even though these data are reassuring, evidence is limited and still inconclusive. To date, breastfeeding during CyA treatment is not recommended because of theoretical risks of immunosuppressive effects in the neonate [203].

Side effects

In a study involving 154 patients with RA, a dose-related decrease in glomerular filtration rate with corresponding increase in serum creatinine has emerged as the most frequently reported side-effect of CyA (48%); after drug discontinuation, creatinine returns within 15% of baseline in almost all

cases [204]. There is a wide variety in the incidence of new-onset arterial hypertension, which ranges from 0 to 57% across available studies. Gastrointestinal symptoms, including nausea, abdominal pain, diarrhoea and vomiting, have been described in less than 5%. Hepatotoxicity (presenting as elevation of hepatic enzymes and bilirubin) usually occurs at higher dosages than those used in rheumatology. Neurologic side effects of CyA include headache, tremor, seizure psychosis, paraesthesias, and sleep disturbances; paraesthesias and tremor can occur in up to 40% of patients. Gingival hyperplasia has been reported in up to 30% of patients on CyA; cutaneous side effects comprise hypertrichosis, epidermal cyst, keratosis pilaris, and sebaceous hyperplasia. Hypertrichosis is rather frequent, presenting in up to 60% of patients. Hyperlipidemia, in particular hypertriglyceridemia, can present in up to 15% of patients [205,206]. Based on epidemiologic analyses, FDA warns about a relationship between CyA and malignant lymphomas among RA patients and about an increased hazard of skin and lymphoproliferative malignancies among patients with psoriasis receiving CyA, even though the relative risk is similar to subjects treated with other immunosuppressive agents [207]. To date, there is no evidence that CyA predisposes to solid malignancies; large controlled studies have even suggested an immunoprotective action of CyA with a decreased OR for breast and colon neoplasias [204]. **Table 11** reports the toxicity profile of CyA in RA patients.

Drug interactions

Table 12 reports the pharmacological compounds interfering with CyA pharmacokinetics. As CyA is mainly metabolized by cytochrome P450, drugs that induce hepatic enzyme metabolism lower CyA concentrations, while drugs that inhibit hepatic metabolism raise CyA blood concentrations. Older age, concomitant renal failure, arterial hypertension and dehydration might also contribute to enhance the nephrotoxicity of CyA [206].

Drug safety monitoring

Due to CyA nephrotoxicity, serum creatinine and blood pressure should be checked on at least two occasions to obtain a baseline value prior to therapy. Both creatinine and blood pressure should be monitored fortnightly during the first 3 months of treatment and monthly thereafter. Dose reduction of 0.5-0.75 mg/kg/day is warranted if serum creatinine increases above baseline by 30% -even if still in the normal range- or if uncontrolled hypertension supervenes. When creatinine increases by more than 50% of baseline, the daily dose dosage should be reduced by 50%; if this reduction does not affect the creatinine value, the drug should be discontinued. If arterial hypertension develops, the use of anti-hypertensive agents should be considered, avoiding potassium-sparing diuretics because of the risk of hyperkaliemia. In case of hyperlipidemia, a lipid-lowering diet should be commenced and a lipid-lowering agent introduced. Since CyA decreases the clearance of statins, rhabdomyolisis may occur, thus warranting strict vigilance. Given that in patients with autoimmune diseases a poor correlation between CyA blood levels and its clinical effect has been noted, the monitoring of CyA plasma concentration is not routinely required [205,206].

Conclusion

CyA exerts a valid immunomodulator action, being effective in the treatment of many autoimmune diseases. Even though novel therapeutic tools have emerged over the recent years, CyA still represents a suitable option in several clinical settings:

a) In SLE, refractory lupus nephritis and cytopenias have been reported to respond well to CyA;
b) In PsA, CyA can be listed as a therapeutic option, being rather effective in cutaneous disease;
c) In BD, CyA is a valued treatment tool in the management of uveitis and thrombophlebitis;
d) In adult onset Still's disease, treatment with CyA can be considered for the most severe complications such as disseminated intravascular coagulation and MAS;

e) In dry eye disease, topical CyA has been proven to be beneficial;

f) In inflammatory myopathies, CyA is currently regarded as a second-line option to be reserved to patients with disease refractory to standard regimen;

g) In paediatric rheumatology, CyA is used in the management of JDM and MAS associated with sJIA.

Conversely, CyA seems to exert an overall poor beneficial effect in SSc, Sjogren's syndrome and systemic vasculitides. CyA can be considered as an anchor drug in particular clinical situations:

a) HCV-positive patients: CyA has been shown to suppress the replication of HCV, and it can thus be administered to those patients with HCV;

b) Pregnancy: CyA can be safely prescribed throughout the gestation course, providing a pharmacological option in pregnant women with an active autoimmune disease.

Surely caution should be paid to CyA safety profile, in particular because of its nephrotoxicity: prescribing this drug should be avoided in patients with a raised baseline creatinine level and uncontrolled hypertension. Unfortunately, most of available evidence about CyA efficacy in rheumatology comes from small and uncontrolled studies, with very few RCT. Nevertheless, available data are encouraging, supporting CyA as a corticosteroid-sparing action in many rheumatologic conditions: despite being regarded as an "out-of-fashion" drug, CyA should be still part of therapeutic armamentarium of rheumatologists, even in 2016.

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Figure 1. Mechanism of action of cyclosporine A.

CyA= cyclosporine A; Ca^{2+}= calcium; NF-ATc-P= phosphorylated cytoplasmic nuclear factor of activated T-cells; NF-ATc= cytoplasmic nuclear factor of activated T-cells; NF-ATn= nuclear nuclear factor of activated T-cells; IL-2= interleukin 2.

Table 1. Clinical studies on cyclosporine A in rheumatoid arthritis.

Author [Ref]	Year	Study design	CyA dose	Follow-up	N of patients	Treatment groups	Outcome
Dougados [5]	1987	CS	5 mg/Kg/day	12 months	12	CyA	Good clinical efficacy
Førre [19]	1987	CC	10 mg/Kg/day	26 weeks	24	CyA AZA	CyA group: improvement in Ritchie index, PI joint circumferences, 50-foot walk time, grip strength AZA group: improvement in grip strength
Weinblatt [7]	1987	CS	6 mg/Kg/day	24 weeks	10	CyA	Significant improvement in joint pain, joint swelling indexes, patient and physician assessments
Dougados [6]	1989	CS	5 mg/Kg/day	12 months	49	CyA	CyA discontinued in 32 patients because of inefficacy or side-effects In 17 patients still receiving CyA, significant clinical improvement persisted at 12-month evaluation
Tugwell [9]	1990	RCT	2.5 mg/Kg/day	6 months	144	CyA Placebo	Significant improvement in CyA group compared to placebo group in joint pain, active joint count, functional status.
van Rijthoven [10]	1991	RCT	5 mg/Kg/day	24 weeks	92	CyA D-penicillamine	CyA and D-penicillamine equally effective
Ahern [18]	1991	RCT	4.2 mg/Kg/day	6 months	52	CyA AZA	CyA and AZA equally effective
van Rijthoven [16]	1991	CS	5 mg/Kg/day	6 months	16	CyA	CyA discontinued in 6 patients because of inefficacy or side-effects In 12 patients still receiving CyA, significant clinical improvement in all considered variables.

Madhok [8]	1991	CS	5 mg/Kg/day	24 months	20	CyA	Significant improvement in Ritchie index, joint pain, CRP, joint function
Bensen [28]	1994	CC	2.5 mg/Kg/day	12 months	40	CyA + gold CyA + MTX	Increased efficacy with the addition of CyA to gold or MTX
Kruger [17]	1994	RCT	5 mg/Kg/day	6 months	117	CyA AZA	CyA and AZA equally effective
Førre [13]	1994	RCT	5 mg/Kg/day	48 weeks	122	CyA Placebo	Slower radiologic progression in CyA group
Tugwell [30]	1995	RCT	2.5-5 mg/Kg/day	6 months	148	CyA + MTX MTX + placebo	CyA + MTX more effective than MTX + placebo in severe RA
Salaffi [29]	1996	CC	2.5 mg/Kg/day	6 months	28	CyA + HCQ CyA + MTX	CyA + MTX more effective and with more side-effects than CyA + HCQ
Pasero [12]	1996	RCT	3 mg/Kg/day	12 months	361	CyA Antimalarials Gold SSZ	Slower radiologic progression in CyA group compared to DMARD group
Bendix [25]	1996	RCT	2.5 mg/Kg/day	6 months	40	CyA + Gold Gold + placebo	CyA + gold as effective as gold + placebo
Stein [36]	1997	CC	2.5 mg/Kg/day	48 weeks	92	CyA + MTX	Clinical improvement with the addition of CyA to MTX
Van de Borne [26]	1998	RCT	1.2.5 mg/Kg/day	24 weeks	88	CyA + chloroquine Chloroquine + placebo	CyA + chloroquine moderately more effective than chloroquine + placebo
Zeidler [14]	1998	RCT	3 mg/Kg/day	18 months	375	CyA Gold	CyA and gold equally effective

Drosos [21]	1998	RCT	3 mg/Kg/day	24 months	103	CyA MTX	CyA and MTX equally effective
Proudman [208]	2000	RCT	1.5 mg/Kg/day	48 weeks	82	CyA + MTX + i.a. steroids SSZ	Similar remission rate in the CyA + MTX + steroid group and in the SSZ group
Drosos [11]	2000	RCT	3 mg/Kg/day	24 months	103	CyA + PDN MTX + PDN	CyA and MTX equally effective in preventing radiological progression
Ferraccioli [37]	2002	CC	3 mg/Kg/day	18 months	126	CyA, then CyA + MTX MTX, then CyA + MTX SSZ CyA + MTX + SSZ	CyA + MTX + SSZ effective in control disease activity
Marchesoni [22]	2002	RCT	3 mg/Kg/day	24 months	57	CyA + MTX, then CyA CyA + MTX, then MTX	MTX more effective than CyA in control disease activity
Gerards [27]	2002	RCT	2 mg/kg/day	48 weeks	120	CyA CyA + MTX	CyA + MTX more effective than CyA in improving disease activity and slowing radiologic progression
Kvien [15]	2002	RCT	5 mg/kg/day	36 months	278	CyA Gold	CyA and gold equally effective in preventing radiological progression
Temekonidis [39]	2002	CS	2 mg/kg/day	12 months	18	CyA + IFX + PDN	Clinical improvement with the addition of CyA to IFX
Marchesoni [33]	2003	RCT	3 mg/kg/day	12 months	61	CyA + MTX MTX	CyA + MTX more effective than MTX in improving disease activity and slowing radiologic progression
Miranda [24]	2004	RCT	2.5-5 mg/kg/day	12 months	149	CyA + chloroquine CyA + placebo	CyA + chloroquine as effective as CyA + chloroquine

Sarzi Puttini [23]	2005	RCT	3 mg/kg/day	12 months	105	CyA CyA + MTX CyA + HCQ	CyA + MTX more effective than CyA and CyA + HCQ in improving disease activity and slow radiologic progression
Karanikolas [31]	2006	RCT	2.5-4.6 mg/kg/day	12 months	106	CyA + LEF CyA LEF	CyA + LEF more effective than monotherapy
Sidiropoulos [38]	2006	CS	2.5-3 mg/kg/day	24 weeks	19	CyA + MTX + IFX	Modest response with CyA + IFX + MTX
Choy [34]	2008	RCT	3 mg/kg/day	24 months	467	CyA + MTX MTX + steroids CyA + MTX + steroids	CyA + MTX + steroids more effective than CyA + MTX and MTX + steroids in slowing radiologic progression
Bejarano [209]	2008	RCT	1.5 mg/Kg/day	7 years	82	CyA + MTX + i.a. steroids SSZ	Better outcome with CyA + MTX + i.a. steroids than with SSZ
Migliore 2010 [40]	2010	CS	2-3 mg/kg/day	6 months	23	IFX + CyA + MTX	CyA + MTX effective in maintaining disease remission obtained with IFX
Hetland [35]	2010	RCT	4 mg/Kg/day	5 years	139	CyA + MTX + HCQ MTX + HCQ + placebo	No clinical benefit from CyA as compared to placebo
Bakker [20]	2010	CC	4 mg/Kg/day	3 months	151	CyA + oral MTX s.c. MTX	s.c. MTX better than CyA + oral MTX in controlling disease activity
Picchianti Diamanti [41]	2012	PC	2-3 mg/Kg/day	12 months	7	CyA + MTX	CyA + MTX effective in maintaining clinical remission after ETN suspension

CyA: cyclosporine A; MTX: methotrexate; AZA: azathioprine; SSZ: sulphasalazine; HCQ: hydroxychloroquine; DMARD: disease-modifying anti-rheumatic drug; PDN: prednisone; IFX: infliximab; ETN: etanercept; CS: case-series; CC: case-control; RCT: randomized controlled trial; CRP: C reactive protein; PI: proximal inter-phalangeal joints; i.a.: intra-articular; s.c.: subcutaneous.

Table 2. Clinical studies on cyclosporine A in psoriatic arthritis.

Author [Ref]	Year	Study design	CyA dose	Follow-up	N of patients	Treatment groups	Outcome
Gupta [47]	1989	CC	6 mg/Kg/day	8 weeks	6	CyA	CyA effective in controlling joint and skin disease
Steinsson [48]	1990	CS	3.5 mg/Kg/day	6 months	8	CyA	CyA effective in controlling joint and skin disease
Salvarani [49]	1992	CS	3 mg/Kg/day	6 months	12	CyA	CyA effective in controlling joint and skin disease
Spadaro [51]	1995	RCT	3-5 mg/Kg/day	12 months	35	CyA MTX	CyA as effective as MTX in disease control
Mahrle [50]	1996	CS	2.7 mg/Kg/day	6 months	55	CyA	CyA effective in controlling joint and skin disease
Macchioni [57]	1998	PC	3 mg/Kg/day	24 months	24	CyA	CyA effective in controlling radiological disease progression in 60% of patients
Salvarani [52]	2001	RCT	3 mg/Kg/day	24 weeks	99	CyA SSZ Symptomatic therapy	CyA more effective than SSZ and symptomatic therapy in disease control
Sarzi-Puttini [56]	2002	PC	3 mg/Kg/day	24 months	60	CyA	CyA effective in disease control
Fraser [53]	2005	RCT	2.5 mg/Kg/day	12 months	72	CyA + MTX MTX + placebo	CyA + MTX more effective than MTX + placebo in disease control
D'Angelo [54]	2010	PC	3 mg/Kg/day	24 week	103	CyA + ETN	CyA + ETN effective in disease control
Atzeni [55]	2011	RCT	3 mg/Kg/day	6 months	41	CyA + ETN MTX + ETN	CyA + ETN as effective as MTX + ETN in controlling joint disease but more effective in controlling skin disease

CyA: cyclosporine A; MTX: methotrexate; SSZ: sulphasalazine; ETN: etanercept; CS: case-series; CC: case-control; RCT: randomized controlled trial; PC: prospective cohort.

Table 3. Studies on cyclosporine A in systemic lupus erythematosus.

Author [Ref]	Year	Study design	CyA dose	Clinical manifestations	Follow-up	N of patients	Treatment group(s)	Outcome
Isenberg [61]	1981	CS	10 mg/Kg/day	Disease activity	7 weeks	5	CyA + steroids	CyA effective in the management of arthralgias in two patients, no improvement in three patients
Feutren [62]	1987	CS	5 mg/Kg/day	Disease activity	12 months	13	CyA	CyA effective in reducing disease activity in 62% of patients
Heule [103]	1986	CR	5.3 mg/Kg/day	Discoid LE	10 weeks	1	CyA + steroids	CyA + steroids not effective in the management of discoid LE
Miescher [63]	1988	CS	5 mg/Kg/day	Disease activity Diffuse proliferative glomerulonephritis	27.1 months	14	CyA + steroids	CyA effective in reducing disease activity and improving kidney function
Favre [73]	1989	PC	5 mg/Kg/day	Unresponsive lupus nephritis	52 months	26	CyA + steroids	CyA effective in reducing disease activity and improving renal function as well as proteinuria in 90% of patients
Balletta [81]	1992	CC	1.5 mg/Kg/day	Active lupus nephritis	12 months	10	Steroids CyA + steroids	CyA + steroids more effective than steroids alone in the management of active lupus nephritis
Hussein [74]	1993	CS	2.24-4.2 mg/Kg/day	Lupus nephritis	35 months	5	CyA + steroids	Systemic and renal flares in 3 of 5 patients
Radhakrishnan [86]	1994	CC	4-5 mg/Kg/day	Membranous lupus nephritis	43 months	10	CyA + steroids	CyA + steroids effective in the management of nephritic syndrome in patients with membranous lupus nephropathy

Miescher [67]	1994	CS	5 mg/Kg/day	Disease activity	7.1 years	73	CyA + steroids +/- MTX +/- CTX	CyA (+/- MTX +/- CTX) effective as steroid-sparing agent
Yell [104]	1994	CR	3.8-4 mg/Kg/day	Discoid LE	24 weeks	2	CyA	CyA effective in the management of discoid LE
Tokuda [64]	1994	CS	3 mg/Kg/day	SLE	20 weeks	10	CyA	CyA effective in reducing disease activity and anti-dsDNA antibody titers
Grabbe [101]	1995	CR	2.5 mg/Kg/day	Subacute LE	12 weeks	1	CyA	CyA effective in the management of subacute LE
Manger [75]	1996	CS	3-5 mg/Kg/day	SLE	64 months	16	CyA	CyA effective in controlling lupus manifestations
Caccavo [65]	1997	CS	2.5-3.5 mg/Kg/day	SLE	24 months	30	CyA	CyA effective in controlling lupus manifestations
Sugiyama [210]	1998	CR	1 mg/Kg/day	Thrombocytopenia	NR	2	CyA + steroids	CyA effective in the management of thrombocytopenia
Dostal [66]	1998	CS	5 mg/Kg/day	Disease activity Lupus nephropathy	12 months	11	CyA + steroids	CyA effective in reducing SLEDAI score, ANA and anti-dsDNA titres, renal histological disease activity and proteinuria
Tam [76]	1998	PC	5 mg/Kg/day	Type IV lupus nephritis	12 months	17	CyA + steroids	CyA + steroids effective in the long-term management of type IV lupus nephritis
Saeki [102]	2000	CR	4 mg/Kg/day	Lupus profundus	3 years	1	CyA + steroids	CyA effective in the treatment of lupus profundus
Bambauer [211]	2000	CS	1-2 mg/Kg/day	SLE	5 years	28	CyA + PE + steroids + AZA +/- CTX	CyA effective in controlling lupus manifestations when associated with PE + steroids + AZA +/- CTX
Morton [69]	2000	CS	4 mg/Kg/day	SLE	3 years	43	CyA	CyA effective in the management of thrombocytopenia but not of other lupus manifestations

								(arthralgia, arthritis, myalgia, fatigue)
Dammacco [68]	2000	RCT	5 mg/Kg/day	SLE	24 months	18	CyA + PDN PDN	CyA effective as steroid-sparing agent in SLE
Hallegua [87]	2000	CS	3.8 mg/Kg/day	Membranous nephritis Disease activity	12 months	10	CyA	CyA effective in reducing proteinuria and and increasing serum albumina, no significant changes in SLEDAI score
Duarte-Salazar [98]	2000	CR	3.5 mg/Kg/day	Pure red cell aplasia	6 months	1	CyA + steroids	CyA effective in the treatment of pure red cell aplasia
Tam [88]	2001	CS	5 mg/Kg/day	Type IV lupus nephritis	48 months	17	CyA + steroids	CyA + steroids effective in lupus nephritis, with reduction of proteinuria, increase of serum albumin and histological improvement
Atzeni [97]	2003	CR	200 mg/day	Pure red cell aplasia	2 years	1	CyA + steroids	CyA effective in the treatment of pure red cell aplasia
Hu [89]	2003	CS	5 mg/Kg/day	Membranous nephropathy	36 months	24	CyA	CyA effective in inducing complete remission in 52.2% of patients, partial remission in 43.3%
Singh [96]	2004	CR	300 mg/day	Aplastic anaemia	4 months	1	CyA + steroids + CTX	CyA effective in the treatment of aplastic anemia
Arcasoy [99]	2005	CR	5 mg/Kg/day	Pure red cell aplasia	3 months	1	CyA + MMF	CyA effective in the treatment of pure red cell aplasia
Wang [95]	2005	CR	3 mg/Kg/day	Refractory haemolytic anaemia	2 months	1	CyA + steroids	CyA effective in the treatment of refractory haemolytic anaemia
Moroni [82]	2006	RCT	4 mg/Kg/day	Proliferative lupus nephritis	4 months	69	CyA AZA	CyA and AZA equally effective as maintenance treatment of proliferative lupus nephritis
Quartuccio [93]	2006	CS	3-5 mg/Kg/day	Thrombocytopenia	23.5 months	6	CyA + steroids	CyA effective in the management of thrombocytopenia
Ogawa	2007	CS	2.5	Refractory lupus	30 weeks	9	CyA + steroids	CyA + steroids effective in

[78]			mg/Kg/day	nephritis				refractory lupus nephritis, with reduction of proteinuria
Rihova [77]	2007	CS	5 mg/Kg/day	Lupus nephritis	85.6 months	31	CyA	CyA effective in reducing proteinuria and stabilizing renal function
Austin [90]	2009	RCT	NR	Membranous lupus nephritis	12 months	42	CyA CTX PDN	CyA more effective than PDN but less effective than CTX in the maintenance treatment of proliferative lupus nephritis
Zavada [83]	2010	RCT	4-5 mg/Kg/day	Proliferative lupus nephritis	18 months	40	CyA CTX	CyA as effective as CTX in the induction and maintenance treatment in patients with proliferative lupus nephritis
Ogawa [79]	2010	CS	2.5 mg/Kg/day	Disease activity	21.5 months	55	CyA	CyA effective in reducing SLEDAI and flare rate
Kamijo [80]	2011	CS	2.5 mg/Kg/day	Proliferative lupus nephritis	2 years	11	CyA	CyA effective as treatment of proliferative lupus nephritis
Zavada [84]	2014	RCT	4.5 mg/Kg/day	Proliferative lupus nephritis	7.7 years	38	CyA CTX	CyA and CTX equally effective at long-term as treatment of proliferative lupus nephritis
Takahashi [100]	2015	CS	NR	Lupus haemophagocytic syndrome	NR	3	CyA + steroids	CyA effective in the treatment of lupus haemophagocytic syndrome

CyA: cyclosporine A; CTX: cyclophosphamide; PDN: prednisone; MTX: methotrexate; AZA: azathioprine; MMF: mycophenolate mofetil; PE: plasma exchange: SLE: systemic lupus erythematosus; LE: lupus erythematosus; SLEDAI: systemic lupus erythematosus disease activity index; NR: not reported; ANA: anti-nuclear antibodies; anti-dsDNA: anti-double stranded DNA antibodies.

Table 4. Studies on cyclosporine A in systemic sclerosis.

Author [Ref]	Year	Study design	CyA dose	Follow-up	N of patients	Treatment groups	Outcome
Zachariae [109]	1990	PC	7.5 mg/Kg/day	16 months	10	CyA	CyA effective in reducing skin thickening in 20% of patients
Clements [108]	1993	PC	5 mg/Kg/day	48 week	10	CyA	CyA effective in reducing skin thickening but not in controlling lung and cardiac involvement
Denton [115]	1994	RCT	2.5 mg/Kg/day	1 year	20	CyA + iloprost Iloprost + placebo	CyA effective in reducing skin thickening and controlling microvascular and oesophageal involvement
Filaci [111]	1999	CR	3-4 mg/Kg/day	-	3	CyA	SRC in all cases
Morton [212]	2000	CS	3.4 mg/Kg/day	-	16	CyA	CyA effective in reducing skin thickening in half of patients
Roch [110]	2004	CR	2 mg/Kg/day	5 years	1	CyA	CyA effective in reducing skin thickening
Zentilin [112]	2004	CR	2.5 mg/Kg/day	6 months	2	CyA	CyA effective in controlling oesophageal involvement
Ando [113]	2013	CR	100-150 mg/day	2-4 years	2	CyA	Stabilization of lung function with CyA as maintenance treatment

CyA: cyclosporine A; SRC: scleroderma renal crisis; CS: case-series; PC: prospective cohort; CR: case-report; RCT: randomized controlled trial.

Table 5. Studies on cyclosporine A in inflammatory myopathies.

Author [Ref]	Year	Study design	CyA dose	Follow-up	N of patients	Treatment groups	Outcome
Grau [116]	1994	CC	5 mg/Kg/day	24 months	10 DM	CyA Steroids + AZA	CyA effective in inducing remissions more quickly than steroids + AZA
Vencovsky [117]	2000	RCT	3-3.5 mg/Kg/day	6 months	20 DM 16 PM	CyA + steroids MTX + steroids	CyA and MTX equally effective in the management of muscle involvement
Kotani [119]	2005	CR	NR	NR	1 DM	CyA + CTX + steroids	CyA + steroids not effective in the management of ILD
Takada [122]	2005	RC	150 mg/day	24 months	53 DM/PM	CyA + steroids Steroids	CyA + steroids more effective than steroids alone in managing PM/DM
Sakamoto [124]	2005	CR	100-150 mg/day	7.5 years	1 DM	CyA + steroids	CyA + steroids effective in the management of ILD
Mii [118]	2006	CR	1 mg/Kg/day	6 months	1 DM	CyA + steroids	CyA + steroids effective in the management of dysphagia
Terao [121]	2007	CR	125 mg/day	4 years	1 DM	CyA + steroids	CyA + steroids effective in the management of pneumomediastinum
Kotani [120]	2008	CS	4 mg/Kg/day	2 weeks	16 DM	CyA + steroids	CyA effective as early treatment of DM-ILD
Kim [213]	2009	CR	100 mg/day	NR	6 DM	CyA + steroids	CyA effective in the management of 5 out of 6 patients with DM complicated by pneumomediastinum
Kotani [214]	2011	CS	4 mg/Kg/day	12 months	14 DM	CyA + steroids	CyA + steroids effective in improving LFT and HRCT

Ingegnoli [127]	2012	CC	5 mg/Kg/day	12 months	15 PM	CyA + steroids CTX + steroids	No significant difference between CyA and CTX groups in the progression rate of ILD at HRCT
Suzuki [126]	2013	CR	150 mg/day	NR	3 DM	CyA + steroids + CTX	CyA + steroids + CTX effective in the management of DM-ILD
Cavagna [125]	2013	CS	3 mg/Kg/day	96 months	18 PM	CyA + steroids	CyA effective in the management of DM-ILD
Labirua-Iturburu [123]	2013	CS	2.5-5 mg/Kg/day	24 months	15 PM	CyA Tacrolimus	CyA effective in the management of DM-ILD

DM: dermatomyositis; PM: polymyositis; ILD: interstitial lung disease; CyA: cyclosporine A; MTX: methotrexate; CTX: cyclophosphamide; AZA: azathioprine; LFT: lung function test; HRCT: high resolution CT scan of the chest; CC: case cohort; RC: retrospective cohort; CS: case-series; CR: case-report; RCT: randomized controlled trial; NR: not reported.

Table 6. Studies on cyclosporine A in systemic vasculitides.

Author [Ref]	Year	Study design		CyA dose	Follow-up	N of patients	Treatment groups	Outcome
Wendling [134]	1985	CR	PMR TA	3 mg/Kg/day	3 months	2	CyA + steroids	CyA effective in the management of relapsing PMR and TA
Gremmel [128]	1988	CR	GPA	5 mg/Kg/day	27 months	2	CyA + steroids	CyA effective of pulmonary and renal involvement
Harley [130]	1990	CR	GPA	NR	6 months	1	CyA	CyA effective in the management of GPA
Borleffs [129]	1990	CR	GPA	5 mg/Kg/day	2 years	1	CyA + steroids	CyA effective in the management of severe GPA with renal involvement
Fullerton [138]	1991	CR	TA	4 mg/Kg/day	3 months	1	CyA	CyA effective in the management of pyoderma gangrenosum associated with TA
Schaufelberger [133]	1998	RCT	GCA	2 mg/Kg/day	6 months	22	CyA + steroids CyA	CyA not effective as additive agent in GCA
McDermott [132]	1998	CR	EGP	3.5 mg/Kg/day	5 months	1	CyA + steroids	CyA effective in the management of severe EGP
Fearfield [137]	1999	CR	TA	5 mg/Kg/day	18 months	1	CyA + steroids + minocycline	CyA effective in the management of pyoderma gangrenosum associated with TA
Horigome [136]	1999	CR	TA	4.3 mg/Kg/day	4 years	1	CyA + steroids	CyA effective in the management of TA
Inoue [131]	2000	CR	GPA	100 mg/day	NR	1	CyA + CTX + steroids	CyA effective in the management of GPA

PMR: polymyalgia rheumatica; GPA: granulomatosis with polyangiitis; GCA: giant cell arteritis; TA: Takayasu's arteritis; EGP: esinophilic granulomatosis with polyangiitis; CyA: cyclosporine A; CTX: cyclophosphamide; CR: case-report; RCT: randomized controlled trial; NR: not reported.

Table 7. Studies on cyclosporine A in Behçet's disease.

Author [Ref]	Year	Study design	CyA dose	N of patients	Follow-up	Treatment groups	Outcome
BenEzra [142]	1988	CC	5 mg/Kg/day	40	3 years	CyA Corticosteroids Leukeran	CyA more effective than conventional treatment in the management of ocular manifestations of BD
Masuda [143]	1989	RCT	10 mg/Kg/day	96	16 weeks	CyA Colchicine	CyA more effective than colchicine in reducing the frequency and severity of ocular attacks, of oral aphthous ulcer and dermal lesions
Ozyazgan [141]	1992	CC	5 mg/Kg/day	23	34 months	CyA CTX	CyA more effective than CTX in the management of BD-associated uveitis at 6 months
Avci [148]	1997	CS	5 mg/Kg/day	24	6 months	CyA	CyA effective on mucocutaneous manifestations of BD
Cantini [147]	1999	PC	5 mg/Kg/day	7	48 months	CyA	CyA effective in the management of thrombophlebitis associated with BD
Yamada [144]	2010	RCT	3-5 mg/Kg/day	37	6 months	CyA IFX	CyA less effective than IFX in reducing episodes of uveitis in BD

BD: Behçet's disease; CyA: cyclosporine A; CTX: cyclophosphamide; IFX: infliximab; CS: case-series; CC: case-control; RCT: randomized controlled trial; PC: prospective cohort.

Table 8. Studies on cyclosporine A in adult onset Still's disease.

Author [Ref]	Year	Study design	CyA dose	Follow-up	N of patients	Treatment group(s)	Outcome
Mori [155]	1993	CR	NR	NR	1	CyA + steroids	Improvement of Still's disease-associated DIC with CyA
Park [156]	2004	CR	2-3 mg/Kg/day	12 months	1	CyA + steroids + IvIg	Improvement of Still's disease-associated DIC with CyA
Hamidou [157]	2005	CR	NR	NR	1	CyA	Improvement of Still's disease-associated haemophagocytic syndrome with CyA
Her [159]	2007	CR	300 mg/day	48 months	1	CyA	Improvement of Still's disease-associated acquired amegakaryocytic thrombocytopenia with CyA
Nagashima [160]	2008	CR	3 mg/Kg/day	NR	2	CyA	Improvement of Still's disease-associated hepatic failure with CyA
Mizrahi [158]	2009	CR	3 mg/Kg/day	8 months	1	CyA + MMF + steroids	Improvement of Still's disease-associated relapsing macrophage activating syndrome with CyA
Mitamura [153]	2009	CS	Adjusted dose	12.4 months	7	CyA	Induction of remission in 6/7 patients with Still's disease

CyA: cyclosporine A; DIC: disseminated intravascular coagulation; NR: not reported; MMF: mycophenolate mofetil; IvIg: intra-venous Immunoglobulins; CR: case-reports; CS: case-series.

Table 9. Studies on cyclosporine A in Sjogren's syndrome or dry eye disease.

Author [Ref]	Year	Study Design	CyA dose	N of patients	Follow-up	Treatment groups	Outcome
Drosos [170]	1986	CS	5 mg/Kg/day	20 SSj	12 months	CyA	CyA effective on xerostomia but not minor salivary gland histology
Drosos [171]	1986	CC	5 mg/Kg/day	20 SSj	6 months	CyA Placebo	CyA effective on histology but not xerostomia
Stevenson [165]	2000	RCT	Topical 0.05% - 0.1% - 0.2% - 0.4%	162 dry eye disease	16 weeks	CyA Placebo	CyA effective on signs and symptoms of xerophtalmia
Sall [167]	2000	RCT	Topical 0.05% - 0.1%	877 dry eye disease	6 months	CyA Placebo	CyA effective on objective and subjective measures of xerophtalmia
Barber [166]	2005	CS	Topical 0.1%	412 dry eye disease	3 years	CyA	CyA safe and effective on xerophtalmia
Roberts [168]	2007	RCT	Topical 0.05%	30 dry eye disease	6 months	CyA Punctual occlusion CyA + punctual occlusion	CyA effective on ocular surface health, additive effects with punctual occlusion
Kim [169]	2009	RCT	Topical 0.05%	150 dry eye disease	3 months	CyA Vitamin A eye drops	CyA as effective as vitamin A eye drops for dry eye disease

CyA: cyclosporine A; SSj: Sjogren's syndrome; CS: case-series; CC: case-control; RCT: randomized controlled trial.

Table 10. Studies on cyclosporine A in macrophage activation syndrome associated with systemic juvenile idiopathic arthritis.

Author [Ref]	Year	Study design	N of patients	Treatment group(s)	Outcome
Mouy [179]	1996	CS	7	CyA	CyA effective as first line or second line tool in MAS
Ravelli [180]	1996	CR	1	CyA	CyA effective as second line tool in MAS
Stephan [181]	2001	CS	18	CyA IvIg Steroids	CyA effective as first and second line tool in MAS associated with sJIA
Sawhney [182]	2001	CS	7	CyA + steroids CTX + steroids Anti-thymocyte globulin + steroids	CyA + steroids effective in MAS
Kounami [183]	2005	CS	5	CyA	CyA effective as second line tool in MAS
Cortis [184]	2006	CS	9	CyA + steroids ETN	CyA + steroids effective in MAS
You [185]	2006	CR	1	CyA	CyA effective as second line tool in MAS
Lin [186]	2012	CS	4	CyA + steroids IvIg + steroids	CyA + steroids effective in MAS

CyA: cyclosporine A; IvIg: intra-venous Immunoglobulins; CTX: cyclophosphamide; ETN: etanercept; CS: case-series; CC: case-control; CR: case-report; MAS: macrophage activation syndrome.

Table 11. The toxicity of cyclosporine A in patients with rheumatoid arthritis [207].

Toxicity	Frequency (%)*
Constitutional symptoms	
Fatigue	3-12%
Fever	0-4%
Influenza-like symptoms	0-6%
Arthralgias/arthritis	0-5%
Reno-urinary toxicity	
Creatine elevation > 30%	13-55%
Creatinine elevation > 50%	3-26%
Dysuria	0-11%
Urinary tract infection	0-19%
Cardiovascular toxicity	
Hypertension	2-26%
Arrythmias	1-6%
Chest pain	1-6%
Gastrointestinal toxicity	
Gum hyperplasia	1-4%
Gingivitis	0-4%
Stomatitis	5-16%
Nausea	14-24%
Vomiting	5-14%
Dyspepsia	4-12%
Anorexia	0-3%
Diarrhea	8-18%
Abdominal pain	7-15%
Skin and appendage toxicity	
Hypertrichosis	0-19%
Alopecia	0-4%
Bullous eruption	0-4%
Rash	7-12%
Purpura	0-4%
Nervous system toxicity	
Dizziness	3-8%
Headache	9-25%
Migraine	0-3%
Paresthesia	1-11%
Depression	1-6%
Insomnia	1-4%
Respiratory toxicity	
Rhinitis	0-10%

Sinusitis	3-8%
Pharingitis	3-6%
Coughing	3-7%
Dyspnea	1-5%
Bronchitis	0-3%
Pneumonia	0-4%

*: considering controlled clinical trials.

Table 12. The interaction of cyclosporine A with other pharmacological compounds.

Increased CyA blood levels	**Decreased CyA blood levels**	**Enhanced nephrotoxicity**
Allopurinol		
Antimalarials		
Bosentan		
Clarythromycin	Barbiturates	
Diltiazem	Carbamazepin	Aminoglycosides
Erythromycin	Rifampin	Amphotericin B
Fluconazole	Rifabutin	Ciprofloxacin
Imatinib	Isoniazid	Sulfonamides
Ketoconazole	Nafcillin	ACE inhibitors
Methylprednisolone (High dose)	Sulfasalazine	
Methotrexate		
Nicardipine		
Verapamil		

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