



PHARMACEUTICALS

VOLUME 100 A
A REVIEW OF HUMAN CARCINOGENS

This publication represents the views and expert
opinions of an IARC Working Group on the
Evaluation of Carcinogenic Risks to Humans,
which met in Lyon, 14-21 October 2008

LYON, FRANCE - 2012

IARC MONOGRAPHS
ON THE EVALUATION
OF CARCINOGENIC RISKS
TO HUMANS

CICLOSPORIN

Ciclosporin was considered by a previous IARC Working Group in 1989 ([IARC, 1990](#)). Since that time, new data have become available, these have been incorporated into the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agent

Chem. Abstr. Serv. Reg. No.: 59865-13-3

Chem. Abstr. Name: Cyclosporin A

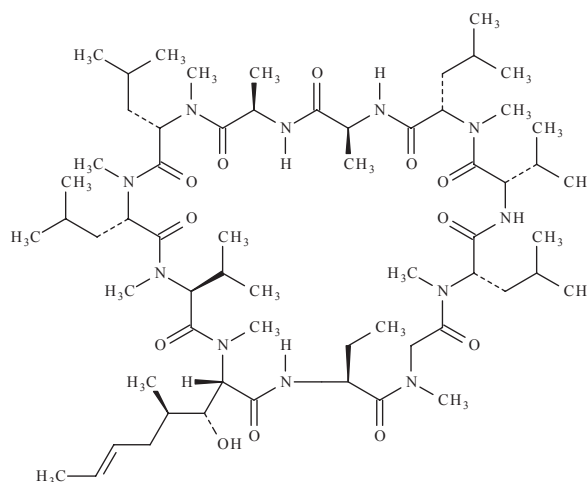
IUPAC Systematic Name:

30-Ethyl-33-[(*E*)-1-hydroxy-2-methylhex-4-enyl]-1,4,7,10,12,15,19,25,28-nonamethyl-6,9,18,24-tetrakis(2-methylpropyl)-3,21-di(propan-2-yl)-1,4,7,10,13,16,19,22,25,28,31-undecazacyclotri-triacontane-2,5,8,11,14,17,20,23,26,29,32-undecone

Synonyms: Cyclo{-[4-(*E*)-but-2-enyl-*N*,4-dimethyl-*L*-threonyl]-*L*-homoalanyl-(*N*-methylglycyl)-(N-methyl-*L*-leucyl)-*L*-valyl-(N-methyl-*L*-leucyl)-*L*-alanyl-*D*-alanyl-(N-methyl-*L*-leucyl)-(N-methyl-*L*-leucyl)-(N-methyl-*L*-valyl)-}; cyclosporin; cyclosporine; cyclosporin A

Description: White prismatic needles ([O'Neil, 2006](#)); white or essentially white, fine crystalline powder ([McEvoy, 2007](#); [Sweetman, 2008](#))

1.1.1 Structural and molecular formulae, and relative molecular mass



Relative molecular mass: 1202.6

1.2 Use of the agent

Information for Section 1.2 is taken from [Royal Pharmaceutical Society of Great Britain \(2007\)](#), [McEvoy \(2007\)](#), [Thomson Healthcare \(2007\)](#), and [Sweetman \(2008\)](#).

1.2.1 Indications

Ciclosporin, a calcineurin inhibitor, is a potent immunosuppressant that is virtually non-myelotoxic but markedly nephrotoxic. It is used in organ and tissue transplantation, for prevention of graft rejection following bone-marrow, kidney, liver, pancreas, heart, lung, and heart-lung transplantation, and for prophylaxis and treatment of graft-versus-host disease. Ciclosporin is also used for the treatment of chronic allograft rejection in patients previously treated with other immunosuppressive agents (e.g. azathioprine).

Oral ciclosporin is used in the management of the active stage of severe rheumatoid arthritis in selected adults who have an inadequate therapeutic response to methotrexate. The drug may be used in combination with methotrexate in those who do not respond adequately to methotrexate monotherapy.

Oral ciclosporin is used in immunocompetent adults with severe (i.e. extensive and/or disabling) recalcitrant plaque psoriasis that is not adequately responsive to at least one systemic therapy (e.g. retinoids, methotrexate, psoralen and ultraviolet A (UVA) light [PUVA] therapy) or in patients for whom other systemic therapy is contraindicated or cannot be tolerated. It is also used to treat atopic dermatitis.

Ciclosporin ophthalmic emulsion is used to increase tear production in adults whose tear production is suppressed secondary to ocular inflammation related to keratoconjunctivitis sicca.

1.2.2 Dosage

Ciclosporin is administered orally as liquid-filled capsules or oral solution. Alternatively, the drug may be administered orally as modified liquid formulations (with increased bioavailability) that form emulsions in aqueous fluids; the modified formulations are available as oral

solutions for emulsion, and as oral liquid-filled capsules.

For the prevention of allograft rejection in adults and children, ciclosporin is administered at 5–10 mg/kg/day. In the postoperative period, dosage is given twice a day. Initial levels are maintained at 250 ng/mL during the first three months followed by a subsequent weaning period as tolerated. For solid organ transplantation, ciclosporin is rarely administered as a single agent. Often, an induction antibody is administered at the time of transplantation with ciclosporin and an antimetabolite (mycophenolic acid or azathioprine). To prevent a cytokine response from the antibody induction agent, an initial dose of steroids is also administered. These steroids are then often eliminated from the treatment. For bone-marrow transplantation, prevention and treatment of graft-versus-host disease, ciclosporin is administered to adults and children over 3 months of age, at a dose of 3–5 mg/kg daily intravenously then converted to 12.5 mg/kg daily orally for 3–6 months then tailed off (may take up to a year after transplantation).

For the treatment of nephrotic syndrome, ciclosporin is administered orally, at a dose of 5–6 mg/kg daily in divided doses. Maintenance treatment is reduced to the lowest effective dose according to proteinuria and serum creatinine measurements, and discontinued after 3 months if no improvement is observed.

For the management of rheumatoid arthritis, the usual initial dosage is 1.25 mg/kg twice daily. Lack of benefit by Week 16 usually leads to the discontinuation of the therapy.

For the management of psoriasis in adults, the usual initial dosage is 1.25 mg/kg twice daily continued for at least 4 weeks unless adverse effects occur. Dosage may be increased in these increments to a maximum of 4 mg/kg daily based on the patient's tolerance and response.

It is also used for the short-term treatment of severe atopic dermatitis (usually less than

8 weeks) in adults and adolescents over 16 years of age.

Ciclosporin is applied topically to the eye as an ophthalmic emulsion in the management of keratoconjunctivitis sicca in adults as one drop of a 0.05% emulsion in each eye twice daily.

1.2.3 Trends in use

The current trend is for minimization of use of calcineurin inhibitors in general.

2. Cancer in Humans

At the time of the previous *IARC Monograph* ([IARC, 1990](#)), both lymphoma and Kaposi sarcoma had been associated frequently with exposure to ciclosporin in case reports of transplant recipients. In two of the five previously reported cohort studies of people receiving ciclosporin for transplant, a higher incidence of lymphoma was identified ([IARC, 1990](#)). In several cases, there was a well-documented regression of lymphoma following withdrawal of the drug ([IARC, 1990](#)). In these studies, the effect of ciclosporin alone is difficult to delineate due to the multiple immunosuppressive drugs administered, the cumulative dose, and the overall global immunosuppression. Since then, new studies have been published, and are summarized below (see Table 2.1 available at <http://monographs.iarc.fr/ENG/Monographs/vol100A/100A-17-Table2.1.pdf>).

[Grulich et al. \(2007\)](#) performed a random-effect meta-analysis of the log of standardized incidence ratios (SIRs) in immunosuppressed patients. In the transplant recipient cohort ($n = 31977$), comparison was made to the general population. [The Working Group noted that these patients were transplanted during the era of three-drug immunosuppression. The majority of the patients would have received ciclosporin, mycophenolic acid mofetil (MMF), and steroids. Steroids are not known to be carcinogenic. The

antimetabolite MMF has known antineoplastic, antireplicative and antiviral properties, and has been shown in several studies to be protective against malignancy development ([O'Neill et al., 2006](#); [Lake et al., 2005](#); [Robson et al., 2005](#)). This leaves ciclosporin as the only possible carcinogenic agent in these mixtures.] For 20 of 28 types of cancers examined, there was a significantly increased risk. Included in these cancers are non-Hodgkin lymphoma, Kaposi sarcoma, squamous cell cancers (skin, oral cavity, vagina, cervix, colon, rectum), and liver cancer. [The Working Group noted the majority of these malignancies are known to have specific viral causes (Epstein-Barr virus, cytomegalovirus, Kaposi sarcoma herpes virus, hepatitis C virus, and several serotypes of human papilloma virus).]

[Väkevä et al. \(2008\)](#) reported on short-term ciclosporin therapy for inflammatory skin disorders, and did not identify any increase in SIRs. [The Working Group noted the short-term and limited drug exposure in this study, which may be the reason for this result.]

[Bustami et al. \(2004\)](#) examined a large cohort of 41000 first-time cadaveric transplant recipients from the Scientific Registry of Transplant Recipients. The use of antibody induction therapy significantly increased the risk for lymphoma and for *de novo* cancers in this study. No effect of either ciclosporin or tacrolimus was noted in patients receiving induction therapy. Ciclosporin patients had a higher relative risk of lymphoma compared to tacrolimus patients when antibody induction was not used.

[Kasiske et al. \(2004\)](#) examined a large cohort of 35765 first-time kidney transplant recipients, and neither ciclosporin nor microemulsion ciclosporin patients had increased relative risks for non-skin cancer (1.01 and 0.98, respectively) or non-melanoma skin cancer (1.02 and 1.01, respectively). [The Working Group noted the large proportion of live donors in this study, which would result in lower requirement for immunosuppression.]

Table 3.1 Studies of cancer in experimental animals exposed to ciclosporin

Species, strain (sex) Duration Reference	Route Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, AKR (M) Up to 34 wk Hattori et al. (1986)	Feed 0, 150 mg/kg in diet daily 30 animals/group	Thymic lymphoma: 0/1, 1/3 at 19 wk 2/12, 13/18 between 20–29 wk 3/9, 9/9 between 30–34 wk	[NS] [$P < 0.004$] [$P < 0.005$]	Screening assay in a strain (AKR) highly susceptible to the development of leukaemia
Rats, Wistar (M) Duration NR Reddi et al. (1991)	Gavage 0, 10 mg/kg bw for 20 wk 13–16/group	Kidney: 2/16, 7/13	[$P < 0.05$]	Diabetes was induced in rats by a single intraperitoneal injection of streptozotocin (60 mg/kg bw). No tumours were observed in a group of 10 non-diabetic control rats
Macaque monkeys (sex NR) Duration NR Bieber et al. (1982)	i.m. 25 mg/kg bw/d for 14 d and then every other day or 17 mg/kg bw/d continuously 16 animals	B-cell lymphoma: 2/16		Intracytoplasmic viral particles found in animals was a concern No untreated control values provided

bw, body weight; d, day or days; i.m., intramuscular; M, male; NR, not reported; NS, not significant; wk, week or weeks

[Opelz & Döhler \(2004\)](#) examined a large cohort of 200000 renal transplant recipients, and reported an 11.8-fold increase in lymphoma in those recipients compared to a matched non-transplant population. In this study, ciclosporin did not confer an increased risk over patients treated with azathioprine/prednisone.

[Kessler et al. \(2006\)](#) examined SIRs in 488 ciclosporin-treated renal transplant recipients. Over 4638 patient-years of exposure, 51 (10.4%) transplant recipients developed a first non-melanoma skin cancer, which was associated with older age at transplant and period of transplant (1991–95). The SIRs for all cancers was 2.2 for men, and 3.0 for women. The SIRs for native renal cell carcinoma was 13.0, for post-transplant lymphoproliferative disorder 9.5, and for cervical cancer 25.3. [The Working Group noted that native renal cell carcinoma has been linked to prolonged end-stage renal disease and haemodialysis, and may be confounding in this study.]

3. Cancer in Experimental Animals

Ciclosporin has been tested in mice and rats by oral administration, alone and in combination with other treatments, and by intramuscular injection in monkeys (macaques) that had received heart or heart-lung transplants (allografts). See [Table 3.1](#)

Mice and rats fed diets containing ciclosporin did not develop an increased incidence of tumours, except in one study where an increased incidence of thymic lymphoma was observed in male mice given ciclosporin alone ([Hattori et al., 1986](#); [IARC, 1990](#)). Two B-cell lymphomas were also reported in 16 macaques receiving ciclosporin via intramuscular injection ([Bieber et al., 1982](#); [Ryffel, 1992](#)).

Renal tumour incidence was increased in streptozotocin-induced diabetic rats administered ciclosporin by gavage ([Reddi et al., 1991](#)).

4. Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

Ciclosporin is rapidly absorbed and widely distributed in humans and in experimental animals ([IARC, 1990](#)). It is extensively metabolized by the cytochrome P450 3A4 (CYP3A4) ([Delaforge et al., 2001](#)). The major route of ciclosporin metabolite excretion is via the biliary system, and renal elimination plays a minor role.

4.2 Cytogenetic effects

In a single study, ciclosporin was reported to increase the incidence of chromosomal aberrations in the lymphocytes of kidney transplant patients. Ciclosporin did not induce dominant lethal mutations in mice, chromosomal aberrations in the bone marrow of Chinese hamsters or micronuclei in the bone marrow of Chinese hamsters or mice *in vivo*. It induced sister chromatid exchange in human peripheral lymphocytes *in vitro* but did not induce gene mutations in Chinese hamster cells. Ciclosporin did not induce mutations in *Salmonella typhimurium* ([IARC, 1990](#)).

4.3 Mechanisms of carcinogenesis

4.3.1 Immunosuppressive activity

Ciclosporin, a cyclic lipophilic undecapeptide, inhibits calcineurin (also known as protein phosphatase 2B). The major effect of this is inhibition of cytokine (and some cell surface receptors) production by activated T cells ([Matsuda & Koyasu, 2000](#); [Rovira et al., 2000](#); [Hamawy, 2003](#); [Mascarell & Truffa-Bachi, 2003](#); [Grinyó & Cruzado, 2004](#)).

The effects of ciclosporin are mediated via inhibition of the nuclear factor of activated T

cells (NFAT) family of transcription factors that regulate inducible cytokine expression. The key interaction is between ciclosporin – bound to its cytoplasmic receptor protein, cyclophilin – and the A subunit of the heterodimeric calcineurin (CnA). Under normal conditions, activation of T cells by engagement of the T-cell receptor with its cognate ligand causes an increase in intracellular Ca^{2+} concentration that activates the calmodulin protein. This activated calmodulin interacts with calcineurin to release an auto-inhibitory domain and activates its latent protein phosphatase activity. In non-stimulated T cells, the three relevant isoforms of NFAT are maintained in a highly phosphorylated form within the cytoplasm. Activation of calcineurin allows dephosphorylation of NFAT and their translocation to the nucleus where these DNA-binding proteins interact with *cis* regulatory elements of activation-induced factors. By binding directly to calcineurin at the interface between the CnA and CnB subunits, the ciclosporin–cyclophilin complex blocks access to the active site of calcineurin, and inhibits its phosphatase activity ([Matsuda & Koyasu, 2000](#)).

The immunosuppressive activity of ciclosporin is consistent with an increased risk for cancer due to impaired immune surveillance, particularly for virus-related cancers such as Epstein-Barr virus-related lymphoma, and cervical cancer which is caused by human papillomaviruses in most cases. However, there are almost certainly other mechanisms involved in the carcinogenic action of ciclosporin. For example, inactivation of interleukin-2 (IL-2) or of NFAT in transgenic mice had an effect on immune function, which is not the same as treatment with ciclosporin, and does not completely explain the carcinogenic effects of ciclosporin observed in humans ([Ryffel et al., 1992](#); [Nabel, 1999](#)).

Furthermore, immunosuppression *per se* cannot explain the peculiar pathological features of the skin cancers found in humans treated with

ciclosporin and other immunosuppressive drugs ([Hojo et al., 1999](#); [Yarosh et al., 2005](#)).

4.3.2 Signalling pathways: relevant effects

(a) Effect on tumour-suppressor growth factor- β (TGF- β)

Ciclosporin also induces increased synthesis of TGF- β and a consequent activation of its dependant transcriptional activators, the (small mothers against decapentaplegic proteins) SMADs ([Hojo et al., 1999](#); [Akool et al., 2008](#)). TGF- β is produced by many tumours and is associated among other things with increased invasiveness ([Teicher, 2001](#); [Bachman & Park, 2005](#); [Leivonen & Kähäri, 2007](#)). Ciclosporin treatment of cultured human pulmonary adenocarcinoma cells causes increased expression of TGF- β and induces changes in properties consistent with acquisition of a more invasive cellular phenotype. In immunodeficient SCID beige mice, ciclosporin treatment was associated with an increased number of pulmonary metastases of a transplanted renal cell adenocarcinoma. Both in-vitro and in-vivo effects were blocked by anti-TGF- β antibodies ([Hojo et al., 1999](#)). These effects on signalling are independent of any immunosuppressive properties of ciclosporin, but they may ultimately contribute to cancer. It seems likely that they are secondary to some other effects of ciclosporin, however.

(b) Oxidative stress and DNA damage

One likely effect of ciclosporin relevant to carcinogenesis is its ability to generate reactive oxygen species (ROS). The literature suggests that antioxidants protect against some of the side-effects (nephrotoxicity, hepatotoxicity, and cardiotoxicity) of ciclosporin ([Rezzani, 2006](#)). In addition, the upregulation of TGF- β (and consequent activation of the SMAD downstream targets) is prevented by antioxidants (specifically *N*-acetylcysteine or superoxide dismutase) ([Akool et al., 2008](#)).

These findings are consistent with the effects of ciclosporin on signalling being secondary to the ability of the drug to induce oxidative stress. Excess ROS generated by ciclosporin indicate the possibility of oxygen radical damage to DNA. This is known to be linked to cancer development. A recent publication ([O'Driscoll & Jeggo, 2008](#)) provides direct evidence that implicates ciclosporin treatment in the induction of DNA double-strand breaks. Importantly, this acute effect was seen in replicating cells that were defective in the repair of DNA double-strand breaks. Ciclosporin, by acting as a source of ROS, causes DNA single-strand breaks that are converted in DNA double-strand breaks during replication. On acute treatment, DNA double-strand breaks only accumulate to detectable levels in repair-defective cells. The implication is that chronic treatment will be associated with increases in DNA double-strand breaks – although in repair-proficient cells, the steady-state levels may fall below the level of detection. Nevertheless, because DNA double-strand breaks are precursors of deletions and/or translocations and chromosomal rearrangements, a chronic, low-level increase in steady-state DNA double-strand break levels is potentially mutagenic and carcinogenic.

In view of the structure and proposed mechanism of ciclosporin, it seems unlikely that it is directly mutagenic by interacting with or damaging DNA. There are several claims that ciclosporin inhibits the repair of ultra-violet-induced DNA damage ([Herman et al., 2001](#); [Ori et al., 2005](#), [Yarosh et al., 2005](#)). The first two studies compared spontaneous or UVC-induced unscheduled DNA synthesis (UDS) in lymphocytes. UDS in lymphocytes from patients treated with triple therapy (ciclosporin/azathioprine/prednisolone) was lower than those from double therapy (azathioprine/prednisolone) or untreated patients. In this same study, UDS induced by UVC in lymphocytes was reduced by ciclosporin treatment *in vitro* ([Herman et al., 2001](#)). In the second

study, ciclosporin was shown to reduce UDS in untreated lymphocytes ([Ori et al., 2005](#)). The third examined DNA cyclobutane–pyrimidine dimer removal which appeared to be reduced, but not abolished by ciclosporin treatment ([Yarosh et al., 2005](#)). Although none of these studies makes an overwhelmingly convincing case for inhibition of DNA repair, UDS measurements are a particularly indirect measure of repair, and the possibility that ciclosporin causes the persistence of promutagenic DNA lesions cannot be discounted until ruled out by a more rigorous experimental approach. These effects would be obviously directly relevant only to ciclosporin-related skin cancers.

(c) Effect on P-glycoprotein

Ciclosporin is also well known as an inhibitor of the function of P-glycoprotein, a membrane-associated transporter that facilitates efflux from the cell of a variety of toxins and anticancer drugs ([Vaalburg et al., 2005](#)). Inhibition of P-glycoprotein function may allow retention in the cell of toxins including potential mutagens, but potentiation of carcinogenic activity has not been demonstrated. However, the doses of ciclosporin used to produce immunosuppression, and the serum levels achieved, are much lower than the concentrations needed to modulate the multidrug resistant (MDR) phenotype *in vitro*, and are also lower than the ciclosporin doses used in clinical trials attempting to decrease resistance to chemotherapy ([List et al., 2001](#); [Ross et al., 1994](#)).

4.4 Synthesis

Ciclosporin is an immunosuppressant and long-term immunosuppression is linked to an increased risk of cancer. There are at least two facets to this. First, immunosuppression *per se* is associated with cancer, for example in individuals positive for the human immunodeficiency

virus (HIV). Pharmacological immunosuppression is associated with an increased incidence of a similar spectrum of malignancies. These generally have a viral etiology ([Grulich et al., 2007](#)). Examples include the EBV-related post-transplant lymphoproliferative disorders ([LaCasce, 2006](#)), and HPV-related cervical carcinoma. In addition to these malignancies that usually arise early after immunosuppression is initiated, there are late effects – such as the development of skin cancer – that may have a different etiology that could reflect direct or indirect effects of ciclosporin on DNA.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of ciclosporin. Ciclosporin causes cancer of the skin (squamous cell carcinoma), cancer at multiple other sites, and non-Hodgkin lymphoma.

There is *limited evidence* in experimental animals for the carcinogenicity of ciclosporin.

Ciclosporin is *carcinogenic to humans* (Group 1).

References

- Akool S, Doller A, Babelova A *et al.* (2008). Molecular mechanisms of TGF beta receptor-triggered signaling cascades rapidly induced by the calcineurin inhibitors cyclosporin A and FK506. *J Immunol*, 181: 2831–2845. PMID:18684975
- Bachman KE & Park BH (2005). Duel nature of TGF-beta signaling: tumor suppressor vs. tumor promoter. *Curr Opin Oncol*, 17: 49–54. doi:10.1097/01.cco.0000143682.45316.ae PMID:15608513
- Bieber CP, Pennock JL, Reitz BA (1982). *Lymphoma in cyclosporine A-treated nonhuman primate allograft recipients*. In: *Malignant Lymphomas*. Rosenberg S, Kaplan H, editors. London: Academic Press, pp. 219–229.
- Bustami RT, Ojo AO, Wolfe RA *et al.* (2004). Immunosuppression and the risk of post-transplant malignancy among cadaveric first kidney transplant

- recipients. *Am J Transplant*, 4: 87–93. doi:10.1046/j.1600-6135.2003.00274.x PMID:14678038
- Delaforge M, Bouillé G, Jaouen M *et al.* (2001). Recognition and oxidative metabolism of cyclodipeptides by hepatic cytochrome P450. *Peptides*, 22: 557–565. doi:10.1016/S0196-9781(01)00364-3 PMID:11311724
- Grinyó JM & Cruzado JM (2004). Cyclosporine nephrotoxicity. *Transplant Proc*, 36: Suppl 240S–242S. doi:10.1016/j.transproceed.2004.01.057 PMID:15041345
- Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM (2007). Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet*, 370: 59–67. doi:10.1016/S0140-6736(07)61050-2 PMID:17617273
- Hamawy MM (2003). Molecular actions of calcineurin inhibitors. *Drug News Perspect*, 16: 277–282. doi:10.1358/dnp.2003.16.5.829315 PMID:12942158
- Hattori A, Perera MI, Witkowski LA *et al.* (1986). Accelerated development of spontaneous thymic lymphomas in male AKR mice receiving cyclosporine. *Transplantation*, 41: 784–787. doi:10.1097/00007890-198606000-00024 PMID:3715967
- Herman M, Weinstein T, Korzets A *et al.* (2001). Effect of cyclosporin A on DNA repair and cancer incidence in kidney transplant recipients. *J Lab Clin Med*, 137: 14–20. doi:10.1067/mlc.2001.111469 PMID:11150019
- Hojo M, Morimoto T, Maluccio M *et al.* (1999). Cyclosporine induces cancer progression by a cell-autonomous mechanism. *Nature*, 397: 530–534. doi:10.1038/17401 PMID:10028970
- IARC (1990). Pharmaceutical Drugs. *IARC Monogr Eval Carcinog Risks Hum*, 50: 1–415.
- Kasike BL, Snyder JJ, Gilbertson DT, Wang C (2004). Cancer after kidney transplantation in the United States. *Am J Transplant*, 4: 905–913. doi:10.1111/j.1600-6143.2004.00450.x PMID:15147424
- Kessler M, Jay N, Molle R, Guillemin F (2006). Excess risk of cancer in renal transplant patients. *Transpl Int*, 19: 908–914. doi:10.1111/j.1432-2277.2006.00383.x PMID:17018126
- LaCasce AS (2006). Post-transplant lymphoproliferative disorders. *Oncologist*, 11: 674–680. doi:10.1634/theoncologist.11-6-674 PMID:16794246
- Lake JR, David KM, Steffen BJ *et al.* (2005). Addition of MMF to dual immunosuppression does not increase the risk of malignant short-term death after liver transplantation. *Am J Transplant*, 5: 2961–2967. doi:10.1111/j.1600-6143.2005.01117.x PMID:16303011
- Leivonen SK & Kähäri VM (2007). Transforming growth factor-beta signaling in cancer invasion and metastasis. *Int J Cancer*, 121: 2119–2124. doi:10.1002/ijc.23113 PMID:17849476
- List AF, Kopecky KJ, Willman CL *et al.* (2001). Benefit of cyclosporine modulation of drug resistance in patients with poor-risk acute myeloid leukemia: a Southwest Oncology Group study. *Blood*, 98: 3212–3220. doi:10.1182/blood.V98.12.3212 PMID:11719356
- Mascarell L & Truffa-Bachi P (2003). New aspects of cyclosporin a mode of action: from gene silencing to gene up-regulation. *Mini Rev Med Chem*, 3: 205–214. doi:10.2174/1389557033488150 PMID:12570836
- Matsuda S & Koyasu S (2000). Mechanisms of action of cyclosporine. *Immunopharmacology*, 47: 119–125. doi:10.1016/S0162-3109(00)00192-2 PMID:10878286
- McEvoy GK, editor (2007). *American Hospital Formulary Service Drug Information*. Bethesda, MD: American Society of Health-System Pharmacists
- Nabel GJ (1999). A transformed view of cyclosporine. *Nature*, 397: 471–472. doi:10.1038/17207 PMID:10028962
- O'Driscoll M & Jeggo PA (2008). CsA can induce DNA double-strand breaks: implications for BMT regimens particularly for individuals with defective DNA repair. *Bone Marrow Transplant*, 41: 983–989. doi:10.1038/bmt.2008.18 PMID:18278071
- O'Neil MJ, editor (2006). *The Merck Index*, 14th ed. Whitehouse Station, NJ: Merck & Co., Inc., p. 461
- O'Neill JO, Edwards LB, Taylor DO (2006). Mycophenolate mofetil and risk of developing malignancy after orthotopic heart transplantation: analysis of the transplant registry of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*, 25: 1186–1191. doi:10.1016/j.healun.2006.06.010 PMID:17045930
- Opelz G & Döhler B (2004). Lymphomas after solid organ transplantation: a collaborative transplant study report. *Am J Transplant*, 4: 222–230. doi:10.1046/j.1600-6143.2003.00325.x PMID:14974943
- Ori Y, Herman M, Chagnac A *et al.* (2005). Spontaneous DNA repair in human mononuclear cells is calcium-dependent. *Biochem Biophys Res Commun*, 336: 842–846. doi:10.1016/j.bbrc.2005.08.186 PMID:16157301
- Reddi AS, Jyothirmayi GN, Halka K, Khan MY (1991). Potentiation of renal tumorigenicity by cyclosporine A in streptozotocin diabetic rats. *Cancer Lett*, 56: 109–115. doi:10.1016/0304-3835(91)90084-U PMID:1825617
- Rezzani R (2006). Exploring cyclosporine A-side effects and the protective role-played by antioxidants: the morphological and immunohistochemical studies. *Histol Histopathol*, 21: 301–316. PMID:16372251
- Robson R, Cecka JM, Opelz G *et al.* (2005). Prospective registry-based observational cohort study of the long-term risk of malignancies in renal transplant patients treated with mycophenolate mofetil. *Am J Transplant*, 5: 2954–2960. doi:10.1111/j.1600-6143.2005.01125.x PMID:16303010
- Ross DD, Wooten PJ, Tong Y *et al.* (1994). Synergistic reversal of multidrug-resistance phenotype in acute myeloid leukemia cells by cyclosporin A and cremophor EL. *Blood*, 83: 1337–1347. PMID:8118035

- Rovira P, Mascarell L, Truffa-Bachi P (2000). The impact of immunosuppressive drugs on the analysis of T cell activation. *Curr Med Chem*, 7: 673–692. PMID:10702633
- Royal Pharmaceutical Society of Great Britain (2007). *British National Formulary*, No. 54. London: BMJ Publishing Group Ltd./RPS Publishing.
- Ryffel B (1992). The carcinogenicity of ciclosporin. *Toxicology*, 73: 1–22. doi:10.1016/0300-483X(92)90166-C PMID:1589877
- Ryffel B, Mihatsch MJ, Fisher GL (1992). Immunosuppression and cancer: the ciclosporin case. *Drug Chem Toxicol*, 15: 95–115. doi:10.3109/01480549209032293 PMID:1597130
- Sweetman SC, editor (2008). *Martindale: The Complete Drug Reference*. London: Pharmaceutical Press. Available at: <http://www.medicinescomplete.com/mc/>
- Teicher BA (2001). Malignant cells, directors of the malignant process: role of transforming growth factor-beta. *Cancer Metastasis Rev*, 20: 133–143. doi:10.1023/A:1013177011767 PMID:11831642
- Thomson Healthcare (2007). *Physicians' Desk Reference*, 61st ed. Montvale, NJ: Thomson.
- Vaalburg W, Hendrikse NH, Elsinga PH *et al.* (2005). P-glycoprotein activity and biological response. *Toxicol Appl Pharmacol*, 207: Suppl257–260. doi:10.1016/j.taap.2005.03.027 PMID:16043202
- Väkevä L, Reitamo S, Pukkala E *et al.* (2008). Long-term follow-up of cancer risk in patients treated with short-term cyclosporine. *Acta Derm Venereol*, 88: 117–120. doi:10.2340/00015555-0360 PMID:18311436
- Yarosh DB, Pena AV, Nay SL *et al.* (2005). Calcineurin inhibitors decrease DNA repair and apoptosis in human keratinocytes following ultraviolet B irradiation. *J Invest Dermatol*, 125: 1020–1025. doi:10.1111/j.0022-202X.2005.23858.x PMID:16297204

