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OVERVIEW

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Update of current immunosuppressive drugs used in clinical organ transplantation

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Abstract The outcome of clinical organ transplantations has improved considerably during the last decade, mainly due to the introduction and administration of new drugs for immunosuppression. Our knowledge of basic immune reactions has led to the development of a variety of new immunosuppressants that promise higher selectivity and additive or synergistic drug effects combined with less toxicity. This article gives a brief update of the immunosuppressives currently used in clinical organ transplantation.

Key words Immunosuppressive drugs

Introduction

In the early days of transplantation, immunosuppressive drugs such as prednisolone, azathioprine, and cyclosporin were successfully used in the clinic to prevent the rejection of grafted organs, but without a clear understanding of their specific molecular mechanisms. The explosive development of immunological research and the intensive investigation of cellular and molecular signalling events and mechanisms have, in recent years, provided greater insight into such immune phenomena as rejection or acceptance and into their modulation by immunosuppressive agents. During the last decade, numerous new immunosuppressive drugs with known immunomodulatory effects have been introduced into experimental and clinical transplantation. This has led to a wide variety of different immunosuppressive drug regimens.

In order to facilitate the clinical assessment and proper placement of the major immunosuppressive drugs used in clinical solid organ transplantation, we have summarized all available data and prepared the present update. It is intended to give the reader a condensed overview of the currently available immunosuppressive drugs for clinical organ transplantation and is an update of previous surveys [6, 19].

Early immunosuppressants

Steroids were the first drugs to be used for immunosuppression. In 1951, Billingham et al. demonstrated that the administration of cortisone could prolong skin graft survival in a rabbit model [1]. The discovery and introduction of 6-mercaptopurine and its derivative azathioprine by Schwartz and Dameshek in 1959 [15] was a milestone in the control of the immune reaction. The combination of steroids and azathioprine, established in 1964, became the first immunosuppressive regimen [3].

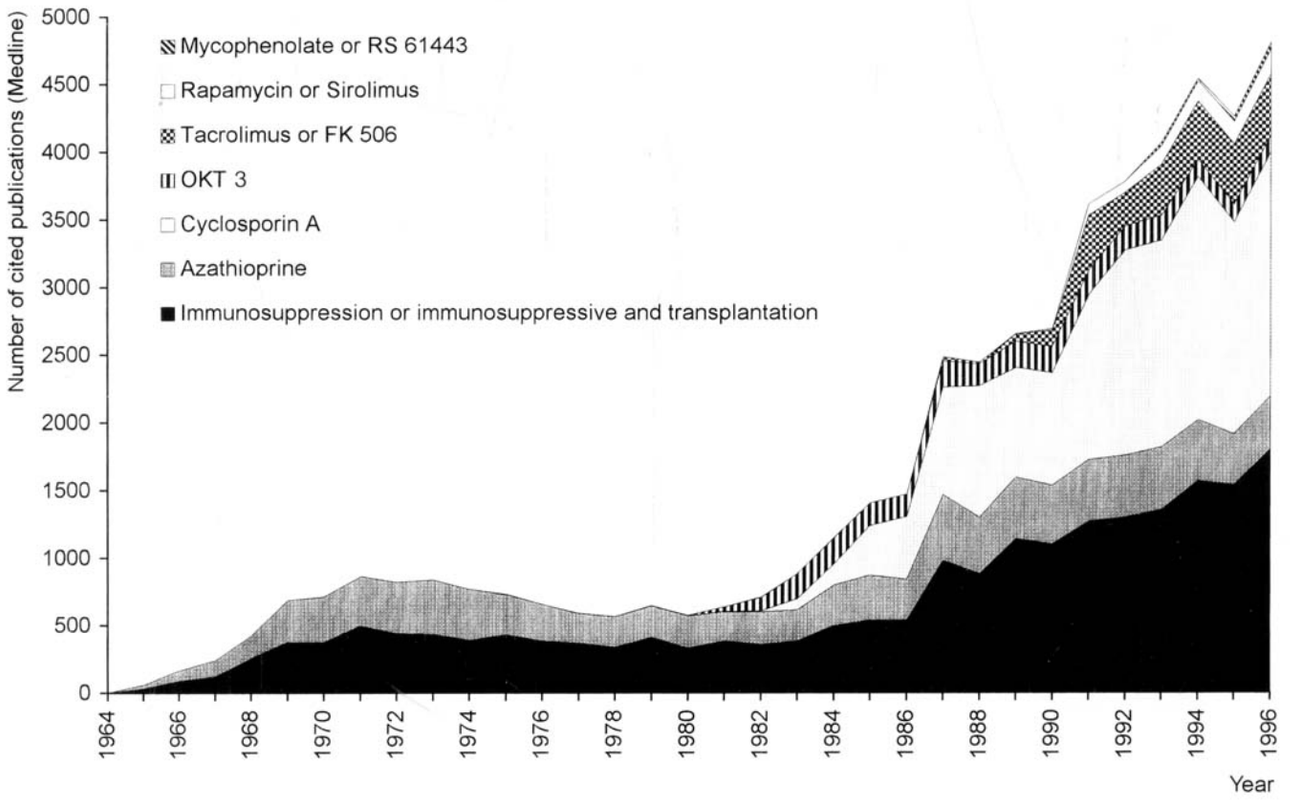

Fig. 1 Development of immunosuppressants in transplantation presented as key word [immunosuppression and transplantation, azathioprine, cyclosporin A, OKT3, tacrolimus or FK506, rapamycin or sirolimus, and mycophenolate mofetil (MMF) or RS 61443] frequency of Medline listed publications from 1964 to 1996. MMF is represented by a small line at the very top of the figure

Latest developments

The discovery of cyclosporin A by Borel in 1972 and its first clinical use by Calne in 1978 revolutionized immunosuppression [2, 4]. Cyclosporin improved patient and graft survival by lowering the incidence of acute rejection episodes in clinical kidney, liver, and heart transplantation. The introduction of monoclonal antibodies like OKT3, a murine monoclonal anti-CD3-receptor antibody, further improved induction and rejection therapy. The side effects of cyclosporin, especially its nephrotoxicity, led to a worldwide search for new immunosuppressive agents with less toxicity. In 1984, tacrolimus, an immunosuppressant with immunosuppressive properties similar to those of cyclosporin, was discovered [7]. The first report on its successful use in rejection therapy after liver transplantation appeared in 1989 [18].

Since then, many new immunosuppressives, including mizoribine, deoxyspergualin, mycophenolate mofetil, rapamycin, brequinar, and leflunomide have been introduced into the field of transplantation, as shown by the increasing number of publications listed each year in Medline (National Library of Medicine, Bethesda, Md., USA; Fig. 1). This immunosuppressive progress has been accompanied by a growing understanding of the basic immune mechanisms leading to rejection as well as to tolerance. The present, as yet unmet, needs of immunosuppression include the use of cyclosporin A and tacrolimus at nontoxic doses, the withdrawal of steroids, and the elimination of anti-T-cell antibodies without increased rejection [13]. Future goals will include the use of drugs for immunomodulation in the sense of graft acceptance and tolerance induction [11].

The T-cell activation cascade, as described previously by Thomson [20], can be used as a basis for the classification of immunosuppressive drugs (Table 1). To facilitate understanding, the details of this update are briefly described. T-cell activation is divided into four phases: (1) APC/MHC-TCR/CD3 interaction, (2) intercellular adhesion molecule interactions, (3) cytokine action at the level of transcription, cytokine release, and signalling, and (4) DNA synthesis and T-cell proliferation [5, 8–10, 12, 16, 17]. The APC/MHC-TCR/CD3 interaction forms the first step of T-cell activation. A second signal, mediated by costimulatory receptors (i.e., B7/CD28), determines whether the T cells become activated or an-

Table 1 *Classification of selected traditional and new immunosuppressive drugs presently used in clinical organ transplantation, according to their mode of action in the different phases of T-cell activation and cell cycle (APC antigen-presenting cell, MHC major histocompatibility complex, TCR T-cell receptor, HSP heat shock protein, IL interleukin, CD cluster of differentiation, mAb monoclonal antibody, pAb polyclonal antibody, LFA lymphocyte function-associated antigen, ICAM intracellular adhesion molecule, NF-ATc cytoplasmatic nuclear factor of T-cell activation, IMP inosine monophosphate, AMP adenosine monophosphate, GMP guanosine monophosphate, IMPDH inosine monophosphate dehydrogenase, DHODH dihydro-orotate dehydrogenase, EMIT enzyme multiplied immunoassay, ELISA enzyme-linked immunosorbent assay, HPLC high-performance liquid chromatography)*

Drug	Synonyms (Manufacturer)	Mode of molecular action	Indication	Dosage drug level	Major side effects
Inhibition of monocyte-macrophage function (APC/MHC-TCR/CD3)					G_0-phase
Deoxyspergualin	Gusperimus, Spanidin (Nippon Kayaku)	Binds to HSP 70; blocks IL-1, IL-6, MHC-II, Ab-production	Induction, rescue therapy hyperacute rejection		Granulocytopenia, gastrointestinal symptoms
Corticosteroids	Prednisolone (Merck)	Blocks APC + T-cell derived expression of cytokines + receptors	Induction, maintenance acute rejection	1 mg/kg per day p.o. 500 mg/day i.v.	Osteoporosis, cataracts, diabetes, obesity
OKT 3	Orthoclone (Cilag)	Anti-CD3, murine mAb	Induction, triple therapy acute rejection	5 mg/day i.v.	Fever, sensitization, lymphoproliferative disorders
ATG	Antithymocyte globulin (Fresenius)	Anti-T-cell, rabbit pAb	Induction, triple therapy acute rejection	5 mg/kg per day i.v.	Fever, sensitization
ALG	Pressimmun (Behring)	Anti-T-cell, horse pAb	Induction, triple therapy acute rejection		Fever, sensitization
Campath 1H	(Glaxo-Wellcome)	Anti-CD52 glycoprotein, humanized rat mAb	Induction		Bronchospasm, hypotension
Inhibition of adhesion molecules (LFA 3-CD 2, CD 80-CD 28, MHC I-CD 8, ICAM 1-CD 11 a/18, MHC II-CD 4)					G_0-phase
Antilfa	Odulimomab (Pasteur-Mérieux)	Anti-LFA 1 (CD 11 a), mouse mAb blocks LFA 1-ICAM 1-interaction	Induction, triple therapy		
Enlimomab	(Boehringer)	Anti-ICAM 1, murine mAb	Maintenance, triple therapy		
BTI-322	(Bio Transplant)	Anti-CD 2, mAb			
Inhibition of cytokine (e.g., IL-2) synthesis (Signal transduction IL-1, IL-1R, IL-6, IL-6R, IL-2, IL-2R)					G_1-phase
Cyclosporin A	Sandimmun, Neoral (Novartis)	Blocks calcineurin phosphatase, NF-ATc translocation	Induction, maintenance	5–10 mg/kg per day p.o. 100–300 µg/l (EMIT)	Nephrotoxicity, hypertension, gingival hyperplasia
Tacrolimus	Prograf, FK506, FR900506 (Fujisawa)	Blocks calcineurin phosphatase, NF-ATc translocation	Induction, maintenance acute rejection	0.1–0.2 mg/kg per day p.o. 3–15 µg/l (MEIA II)	Neuro- and nephrotoxicity, diabetes
Sirolimus	Rapamycin, Rapamune (Wyeth-Ayerst)	Blocks p70 S6-kinase	Induction, maintenance chronic rejection		Gastrointestinal symptoms
SDZ-RAD	40-0-(2-hydroxyethyl)-RPM (Novartis)	inhibits growth factor-driven cell proliferation [14]			
CHI 621	Simulect (Novartis)	Anti-IL-2R (CD25), chimeric mouse/human mAb	Induction, triple therapy		
Leukotac	BT 563 (Biotest)	Anti-IL-2R, mouse mAb	Induction, triple therapy		

Table 1 *(Continued)*

Drug	Synonyms (Manufacturer)	Mode of molecular action	Indication	Dosage drug level	Major side effects
Inhibition of DNA synthesis		(Translation, T-cell proliferation)			S-phase
Azathioprine	Imuran (Wellcome)	Prodrug (6-mercaptopurine), blocks conversion of IMP to AMP/GMP	Induction, maintenance, triple therapy	1–2.5 mg/kg per day p.o.	Myelo- and hepatotoxicity
Cyclophosphamide	Endoxan (Asta)	Blocks mitosis	Induction, maintenance, triple therapy	1–5 mg/kg per day i.v.	Leukopenia, cystitis, alopecia, cardiotoxicity
Mycophenolate mofetil	Cell cept, RS 61443 (Hoffmann-La Roche)	Prodrug (mycophenolic acid), blocks purine de novo synthesis (IMPDH)	Induction, maintenance, chronic rejection	20–40 mg/kg per day p.o.	Gastrointestinal symptoms, myelodepression
Brequinar sodium	BQR, DUP 785 (Dupont-Merck)	Blocks pyrimidine de novo synthesis (DHODH)	Rescue therapy		Myelodepression, mucositis
Mizoribine	Bredinin, MZR (Sumitomo)	Prodrug (MZR-5'-monophosphate), blocks purine de novo synthesis (IMPDH)	Induction, triple therapy		Leukopenia
Leflunomide	HWA 486, LFM (Hoechst)	Blocks tyrosine kinase, IL-2 signal transmission, xeno-Ab-synthesis	Chronic rejection, xenotransplantation		

ergic. After receiving the proper second signal, cytokine release (i.e., interleukin-2) and cytokine receptor expression lead to an amplification of T-cell activation and proliferation. Activated lymphocytes infiltrate the graft and attack the foreign antigen.

The boxes on the left side of Table 1 illustrate the T-cell activation step that is inhibited by the immunosuppressant; on the right side, the corresponding cell cycle phase is shown. The first column displays the drug's generic name. The second column presents the synonyms, trade names, and the manufacturers. The third column specifies the proposed mode of molecular action. Indications for the clinical use of the immunosuppressant are given in the fourth column, divided into prophylactic administration: induction and maintenance, the therapeutic indication for rejection, and the kind of combination such as "triple therapy". Combinations may be advisable if additive or synergistic effects allow dose reduction and, consequently, limit drug-induced side effects. The fifth column indicates the dosages recommended in the literature or used at our centre, as well as the need of drug level monitoring with method and target range. Therapeutic drug monitoring (TDM) would appear to be essential, especially for cyclosporin A and tacrolimus, to prevent drug-induced toxicity. Which method of TDM should be performed for each drug is still under investigation. However, when therapeutic drug levels are recommended, it is essential also to specify the analytical method which, ideally, should have a high specificity for the parent drug. We have indicated the preferred methods used at our institution. The last column summarizes the major drug-specific side effects.

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