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ESOT update on immunosuppressive substances in clinical development or use 1995

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Abstract The ESOT Council conducted an inquiry on new immunosuppressive substances in order to help keep members of ESOT informed. Thirty-one pharmaceutical companies were sent a questionnaire indicating whether they were developing new immunosuppressive substances/antibodies. Sixteen companies responded: 11 furnished information on 16 substances; 5 said that they were not developing any new immunosuppressive agents. Fifteen companies did not reply at all. The results of the first inquiry are reported here.

Introduction

During the General Assembly meeting of the European Society for Organ Transplantation (ESOT) in 1993 in Rhodes, the Council received the request to conduct an inquiry on new immunosuppressive substances and to report their findings during the following General Assembly meeting in 1995 in Vienna. The underlying reason for this was concern about the rapidly proliferating development of new immunosuppressive agents and the growing difficulty for the members of ESOT to remain informed.

The Council agreed to conduct regular inquiries and to deliver a brief summary of the current status of new immunosuppressive substances during the biannual congresses of the ESOT. At the Council meeting in Frankfurt in December 1995, the decision was made to publish these reports in *Transplant International*. This is the report of the first inquiry.

Materials and methods

Thirty-one pharmaceutical companies were approached by the ESOT Council in May 1995 and asked to fill out a detailed form indicating whether they were developing new immunosuppressive substances/antibodies. If so, they were asked to indicate in which phase of development the substances were at that moment. They were also asked about the putative mechanism of the substance, how much experience they had with it (i.e., approximately how many patients and centers were using it), and the indication for treatment. Finally, the companies were asked to provide at least one reference.

Sixteen companies responded to the inquiry. Eleven companies – Biotest, Bio Transplant, Boehringer Ingelheim, Fresenius, Fujisawa, Hoechst, Hoffmann-La Roche, Mérieux, Sandoz, Smith-Kline Beecham, and Wyeth-Ayerst – reported on 16 substances. Five companies – Glaxo, Merck, Opopharma, Schering, and Wellcome – denied that they were developing new immunosuppressive agents. Fifteen other companies – Baxter, Behring, Berna, Boehringer Mannheim, Ciba-Geigy, Cilag, Du Pont, Immuno, Lederle, Organon, Parke Davis, Pfizer, Rhone-Poulenc, Searle, and Upjohn – did not reply at all. The ESOT Council regrets that these companies did not take advantage of this opportunity to freely publicize their products and hopes that they will participate in the next inquiry in 1997.

What follows is a reproduction of the answers given by the participating pharmaceutical companies to the questions included on the inquiry during the period June to July 1995.

Results

New antibodies in development

1. *Name:* **anti-CD4 mAb (SB 210396)**
   Producer: SmithKline Beecham Pharmaceuticals
   Description: Humanised primate mAb to the lymphocyte surface antigen CD4
   Mechanism: Demonstrated immunomodulatory activity *in vitro* and in animal models *in vivo*.
   In phase I clinical trials, has demonstrated transient T-cell depletion and downregulation of T_{helper} cell phenotype
   Phase: Entering phase 3
   Experience with: (no answer)
   Tested: Combined with background steroid (maximum 10 mg) and NSAIDs, against placebo
   Reference: Newman R et al. Biotechnology 10, 1992, 1455–1460; Yocum DE et al. Arthritis and Rheumatism, 37: S336, 1994 – Sollinger AM et al. Arthritis and Rheumatism, 37: S337, 1994

2. *Name:* **Antilfa (Odulimomab)**
   Producer: Pasteur-Mérieux IMTIX
   Description: Anti-LFA-1 α subunit (CD 11 a); mouse IgG 1
   Mechanism: Blocks interaction LFA-1 / ICAM-1
   Modulation of LFA-1
   Nondepleting mAb
   Phase: Phase 2 completed, phase 3 ongoing
   Experience with: 20 centers
   Tested: For induction therapy, combined with triple therapy (sequential, against triple therapy combined)
   Reference: (not given)

3. *Name:* **ATG-S-Fresenius S (new modified)**
   Producer: Fresenius AG
   Description: Polyclonal rabbit Ab against T lymphocytes
   Mechanism: Same as ATG (Fresenius)
   Phase: Replacing ATG on the market
   Experience with: (no answer)
   Tested: (no answer)
   Reference: (not given)

4. *Name:* **BTI-322**
   Producer: Bio Transplant Inc
   Description: Anti-CD2 monoclonal antibody
   Mechanism: Blocks T-cell activation by binding CD2 (COCD2a) and induces hyporesponsiveness during T-cell antigen challenge
   Phase: Ongoing phase 2 trial
   Experience with: (no answer)
   Tested: (no answer)
   Reference: Giovino-Barry VC et al. FASEB J 9: A232, 1995

5. *Name:* **CHI 621**
   Producer: Sandoz Pharma AG
   Description: Chimeric mouse/human monoclonal antibody with specificity for IL-2R (CD25)
   Mechanism: As with all substances with binding of Ab to IL-2R; prevents IL2-mediated proliferation of T cells
   Phase: Phase 3 ongoing
   Experience with: 750 patients, 38 centers
   Tested: For induction therapy combined with dual I/S therapy, Neoral, steroids, against placebo
   Reference: Strom TB, IMM Reviews 1992, 129: 131–163

6. *Name:* **Enlimomab**
   Producer: Boehringer Ingelheim AG
   Description: Monoclonal antibody, murine IgG_{2a}
   Mechanism: Anti-ICAM-1 monoclonal antibody
   Phase: Ongoing phase 3 trial
   Experience with: > 600 patients in > 30 centers
   Tested for: Maintenance immunosuppression combined with triple therapy against placebo control trials
   Reference: (not given)

7. *Name:* **Leukotac (BT563)**
   Producer: Biotest Pharma GmbH
   Description: Mouse monoclonal IgG1 anti human IL-2-receptor (α-chain) antibody.

Mechanism:	Blocks IL-2-receptor and consequently inhibits clonal expansion of antigen-activated cytotoxic T lymphocytes
Phase:	Ongoing phase 3 trial
Experience with:	About 600 patients in 15 centers
Tested:	For induction therapy, combined with ciclosporin, glucocorticoids (azathioprine) against ATG, placebo, OKT3
Reference:	(not given)

8. *Name:*	**Monoclonal rat-AB-cocktail**
Producer:	Fresenius AG
Description:	Anti-CD5 and anti-CD7
Mechanism:	(no answer)
Phase:	(no answer)
Experience with:	(no answer)
Tested:	(no answer)
Reference:	(not given)

9. *Name:*	**Zenapax, HAT (Daclixi mab)**
Producer:	Hoffmann-La Roche
Description:	Recombinant monoclonal immunoglobulin of the human IgG1 isotype
Mechanism:	Zenapax or humanized Anti Tac. recognizes the IL-2- RTAC protein and inhibits IL2-mediated biological responses of activated lymphoid cells
Phase:	Entering phase 3
Experience with:	516 patients, 40 centers
Tested:	For maintenance immunosuppression, combined with CyA, corticosteroids, against placebo controlled
Reference:	Anasetti C et al.: Treatment of acute graft versus host disease with a humanized monoclonal antibody specific for IL-2R. Blood 1992, 80: 373A

New compounds in development

1. *Name:*	**Azaspirane SKF 106615 (MTAC)**
Producer:	SmithKline Beecham Pharmaceuticals
Description:	Azaspirane/macrophage targeting anti-arthritic compound (MTAC)
Mechanism:	(no answer)
Phase:	Phase 1 ongoing
Experience with:	(no answer)
Tested:	(no answer)
References:	Badger AM and Wright C. SKF-106615 dihydrochloride. Drugs of the Future (in press) Herzyk DJ et al: Modulation of murine host defense against candida albicans infection by the azaspirane SK&F 106615. 9th Int. Congress Immunology, July 23–29, 1995 (in press) Kupiec-Weglinski JW and Badger AM: In "Immunosuppressive drugs in organ transplantation: basic immunology and clinical, experience". Eds. Venkataramanan R and Starzl T (in press) Badger AM: 4th Ann. Rheumatoid Arthritis Conference, Dec. 1–2, 1994 (Washington) Badger AM et al.: 4th Biannual Congress Int. Soc. for Rheumatic Therapy, May 5–7, 1994 (Washington)

2. *Name:*	**CellCept (mycophenolate mofetil)**
Producer:	Hoffmann-La Roche
Description:	Antimetabolite
Mechanism:	(no answer)
Phase:	Phase 3 completed
Experience with:	2500 patients in about 100 centers
Tested:	For rejection treatment; for maintenance immunosuppression, combined with CyA and steroids against CyA, azathioprine, and steroids, or CyA steroid and placebo
References:	Morris RE et al: Transplant Proc 1990, 22: 1659–62 Platz K, Sollinger HW et al: Transplantation 1991, 51: 27–31 Platz K et al: Surgery 1991, 110: 736–41 Deierhoi MH et al. Am Surg 1993, 217: 476–84 Pichlmayr R et al. Lancet 27/5/95; 345: 1321–25

3. *Name:*	**Leflunomide**
Producer:	Hoechst AG
Description:	(no answer)
Mechanism:	(no answer)

Phase:	Preclinical stage; phase 1 not yet entered
Experience with:	(no answer)
Tested:	(no answer)
Reference:	(not given)

4. *Name:* **Prograf/Tacrolimus/FK506**

Producer:	Fujisawa GmbH
Description:	Macrolide lactone with potent in vitro and in vivo immunosuppressive activity
Mechanism:	Studies suggest that Prograf inhibits the formation of cytotoxic lymphocytes, which are regarded as being primarily responsible for graft rejection. Prograf suppresses T-cell activation and T-helper cell-dependent B-cell proliferation, as well as the formation of lymphokines such as interleukins-2 and -3 and gamma-interferon and the expression of the interleukin-2-receptor. At the molecular level, the effects of Prograf appear to work by binding to a cytosolic protein (FKPB), which is responsible for the intracellular accumulation of the compound.
Phase:	Phases 1–3 completed, phase 4 ongoing in four countries
Experience with:	About 1400 patients in about 50 centers in Europe
Tested:	For induction therapy, for rejection treatment, for maintenance immunosuppression, combined with steroids and azathioprine and ATG/ALG/OKT3 against cyclosporin A
References:	Peters DH et al.: Tacrolimus: a review of its pharmacology, and therapeutic potential in hepatic and renal transplantation. Drugs 1993; 46(4): 746–794 Schreiber SL and Crabtree GR: The mechanism of action of cyclosporin A and FK506. Immunol. Today 1992; 13(4): 136–142.

5. *Name:* **RAD666**

Producer:	Sandoz Pharma AG
Description:	Macrolide of the rapamycin class
Mechanism:	Inhibition of T-cell proliferation by blocking signal transduction from IL-2 receptor
Phase:	Entering Phase 1
Experience with:	(no answer)
Tested:	(no answer)
Reference:	Kahan BD, Clin Transpl 7: 113–125, 1993

6. *Name:* **Sandimmun Neoral**

Producer:	Sandoz Pharma AG
Description:	New formulation, microemulsion, of Sandimmun^R
Mechanism:	As recognized for cyclosporin with improved pharmacokinetic properties
Phase:	Phase 4 ongoing in 43 countries
Experience with:	> 1500 patients, > 100 centers
Tested:	For maintenance immunosuppression, combined with various regimens, against Sandimmun^R
Reference:	Holt DW et al.: Sandimmun Neoral pharmacokinetics: impact of the new oral formulation. Transplant Proc 1995, 27: 1434–1437

7. *Name:* **Sirolimus (rapamycin)**

Producer:	Wyeth-Ayerst
Description:	Macrolide antibiotic isolated from *Streptomyces hygroscopicus*
Mechanism:	Inhibits proliferation of lymphocytes by blockade of cytokine-driven signal transduction, specifically S6 and cyclin-dependent kinases, which are key pathways required for protein and DNA synthesis
Phase:	Phase 2 partially completed, partially ongoing
Experience with:	(no answer)
Tested:	(no answer)
Reference:	Morris RE, Transplantation Reviews 6: 39–87 1992

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