CHAPTER 4
Immunosuppressive therapy and monitoring

CHAPTER 4.1 Immunosuppressive induction therapy

Burkhard Tönshoff[1], Lars Pape[2] & Jan Dudley[3]

[1] Heidelberg University, Medical Faculty Heidelberg, Department of Paediatrics I, University Children's Hospital, Heidelberg, Germany
[2] Department of Paediatrics II, University Hospital of Essen, Essen, Germany
[3] Bristol Royal Hospital for Children, Bristol, United Kingdom

ORCIDs:
Burkhard Tönshoff: https://orcid.org/0000-0002-6598-6910
Lars Pape: https://orcid.org/0000-0002-3635-6418
Jan Dudley: https://orcid.org/0000-0002-8066-6739

1 Basiliximab

The humanised anti-interleukin-2 receptor antibody basiliximab (Simulect®) is available for the prophylaxis of acute rejection episodes as part of induction therapy and is routinely administered in some countries (e.g., the United Kingdom [UK]) for prevention of acute rejection. Binding of IL-2 to the IL-2 receptor initiates a cascade of intracellular signals leading to functional differentiation of T cells and cell proliferation. The association of the constitutively expressed alpha-chain of the receptor and beta-chain is required for the formation of the IL-2 binding site, but this is only expressed on activated T cells and a subpopulation of B cells and antigen-presenting cells. Therapy with anti-IL-2 receptor antibodies therefore only blocks the antigen-activated T cells.

Studies of cyclosporine- and steroid-based maintenance immunosuppressive regimens without MMF or everolimus have shown that basiliximab reduces acute rejection compared with no induction (Cransberg et al. 2008; the Network meta-analysis of RCTs in adults). However, no prospective studies have shown that basiliximab has the same effect on reducing the incidence of acute rejection, when the maintenance regimen is based on tacrolimus and/or MMF.

Published in: Tönshoff & Pape (eds.), Management of the paediatric kidney transplant recipient. Heidelberg: heiBOOKS 2026, pp. 87–92. DOI: https://doi.org/10.11588/heibooks.1732.c25446

In fact, two prospective randomised trials in paediatric kidney transplant recipients at low or moderate immunological risk failed to demonstrate an additional benefit of basiliximab in preventing acute rejection compared with a regimen of tacrolimus, azathioprine and steroids or a regimen of cyclosporine A, mycophenolate mofetil (MMF) and steroids (Grenda et al 2006, Offner et al 2008). In Europe, basiliximab is particularly indicated when other immunosuppressive drugs, e.g., glucocorticoids, are to be stopped early, i.e., from day 5 post-transplant (see Chapter 5.1). Some centres give basiliximab induction therapy with early use of low-dose CNI in combination with everolimus.

Recommended dose: in children > 35 kg is 20 mg, in children ≤ 35 kg 10 mg basiliximab as a short infusion over 30 min given intravenously 1 hour preoperatively; the second dose is given on day 4 after transplantation.

Half-life of basiliximab in children and adolescents receiving MMF is approximately 10 weeks, without MMF approximately 5 weeks (Höcker et al 2008).

Side effects: Rare. Severe acute (within less than 24 hours) hypersensitivity reactions were observed both on initial application of basiliximab and on re-application during a further treatment cycle. These included anaphylactoid reactions such as rash, urticaria, pruritus, sneezing, wheezing, hypotension, tachycardia, dyspnoea, bronchospasm, pulmonary oedema, heart failure, respiratory insufficiency and capillary leak syndrome. If a severe hypersensitivity reaction occurs, treatment with basiliximab must be discontinued permanently and no further application must be carried out. There is a small risk of hypersensitivity reactions in a subgroup of patients who receive further doses of basiliximab for subsequent transplants.

2 Lymphocyte-depleting antibodies

The two polyclonal anti-thymocyte globulin (ATG) preparations Thymoglobulin® and Grafalon® (formerly ATG-Fresenius®) and the monoclonal anti-B-cell antibody rituximab are currently available as lymphocyte-depleting antibodies in transplantation medicine in Europe. Thymoglobulin® is produced from rabbits immunised with human thymocytes; the antithymoglobulin recognises and destroys human T-lymphocytes and thus acts by removing T-lymphocytes from the bloodstream, modulating T-cell activation and so-called T-cell homing. The

production of Grafalon® is based on the immunisation of rabbits with the Jurkat T-lymphoblast cell line.

A network meta-analysis of RCTs in adults showed that ATG (Thymoglobulin®) reduces acute rejection compared with treatment without induction, but treatment is longer and more complex than with basiliximab, and that adults having Thymoglobulin® have more adverse events (including post-transplant lymphoproliferative disorder) than those having basiliximab (NICE 2017). For this reason, indications for ATG as induction agents are limited to those at high immunological risk of an early acute rejection reaction.

ATG contains a variety of antibodies with broad specificity and therefore does not have a single mechanism of action. In addition to T cell-specific antibodies (CD2, CD3, CD4, CD5, CD8, CD25, CTLA-4), which suppress the T cell-mediated immune response, ATG contains specific antibodies against activated B cells (CD19, CD20, CD21), but also against adhesion molecules (CD11a, CD18) and cell line-unspecific markers such as ß2-microglobulin and HLA-DR. In addition, ATG contains antibodies against monocytes, natural killer cells and transduction molecules (CD45). Many of the antibodies in ATG, despite purification, also recognise antigens expressed on non-lymphoid cells such as erythrocytes, neutrophils, platelets and endothelial cells. Thus, despite the name implying lymphocyte specificity, ATG is not specific for any cell type.

Indications:

- high immunological risk of an early acute rejection, such as highly immunised patients with a panel-reactive HLA antibody titre > 80% (see Chapter 5.2).
- steroid-resistant rejection that do not respond to intravenous bolus administration of glucocorticoids (see Chapter 6.1).

The dosage of Thymoglobulin® is patient-adjusted with cell monitoring to successfully treat rejection while avoiding excessive immunosuppression. The initial dose is 1.5 mg/kg per day, with subsequent doses administered on alternate days over 3–5 days based on total lymphocyte count or total T-lymphocyte count (CD3+).

Recommended dosage:

1st loading dose: 1.5 mg/kg Thymoglobulin®,
2nd maintenance dose (administer over 3–5 days on alternate days):

Maintain dose if:	Total lymphocytes > 100/µl <300/µl or CD3+ or CD2+ > 10/µl < 50/µl.
Reduce the dose if:	Leucocyte count between 2,000 and 3,000 Platelet count between 50,000 and 75,000
Stop the dose if:	Total lymphocytes < 100/µl or CD3+ or CD2+ < 10/µl Leukocyte count below 2,000 Platelet count below 50,000
Increase the dose (e.g., 2 mg/kg) if:	Total lymphocytes > 300/µl or CD3+ or CD2+ > 50/µl.

The maximum cumulative dose of 8 mg/kg thymoglobulin should not be exceeded. If limit values such as total lymphocytes 120/µl or CD3+ 20/µl are measured, the dose may be reduced to 0.75 mg/kg.

Important:

- An ongoing infection should be ruled out before administration: medical history, physical examination, differential blood count, C-reactive protein, urinalysis, chest x-ray if necessary.
- Treatment with this drug requires close clinical monitoring of the patient: The first dose of Thymoglobulin® should be administered in the intermediate or intensive care unit. Some centers recommend that the patient should be fasting in the morning. The infusion is placed and started by the physician. During the infusion period, the patient is monitored as follows and vital signs are recorded on a monitoring sheet:
  - Monitor until the following morning,
  - Blood pressure taken initially every 15 minutes, then every 30 minutes until 2 hours after completion of the infusion,
  - Temperature taken at least twice.

According to the calculated dose, administer per manufacturer instructions via a central vein catheter for 4 hours (or longer if there is a hypersensitivity reaction (see below)).

Co-medication:

- All patients should receive an antihistamine (clemastin 0.04 mg/kg body weight i.v.) one hour prior to thymoglobulin administration.
- (Methyl)prednisolone 2–7 mg/kg i.v. should be given at least 30 minutes before the first dose of thymoglobulin.
- If the first dose is well tolerated, methylprednisolone can be omitted for the subsequent doses on days 3 and 5.
- At least 30 minutes before thymoglobulin administration, esomeprazole (Nexium®, dosage: patients aged 1–11 years: 10–20 kg bw – 10 mg/d; > 20 kg bw – 10–20 mg/d, patients aged 12–18 years: 20–40 mg/d) is given as short infusion.
- Paracetamol should be administered at least 30 minutes prior to the administration of thymoglobulin:
  - In children > 3 months and < 10 kg bw: 7.5 mg Paracetamol/kg as a short infusion
  - for body weight of 10–50 kg: 15 mg Paracetamol/kg as short infusion
  - for body weight of > 50 kg: 1 g Paracetamol as a short infusion

Adverse effects:

Immediately at the start, during or shortly after the infusion of thymoglobulin, anaphylactoid reactions may occur, such as a drop in blood pressure, a feeling of tightness in the chest, fever and urticaria. These symptoms are usually more severe with the first infusion of thymoglobulin and disappear with subsequent infusions. However, if the reactions are clinically significant, thymoglobulin treatment must be discontinued and anaphylaxis or shock therapy initiated. Similar to the use of other heterologous antisera, serum sickness may occur after 8 to 14 days of thymoglobulin treatment. If the symptoms are mild and reversible, there is no need to discontinue thymoglobulin therapy.

Infection prophylaxis:

- Except for CMV-negative donors and CMV-negative recipients, prophylaxis with valganciclovir in a prophylactic dosage for 6 months is required for all other constellations (see Chapter 7.1).
- Pneumocystis jirovecii prophylaxis with cotrimoxazole for 6 months (see Chapter 7.4).

References

1 Cransberg K, Bouts AH, Cornelissen EA, Lilien MR, Van Hoeck KJ, Hop WC, Nauta J. Recovery of graft function in pediatric kidney transplantation is not affected by delayed introduction of cyclosporine. Transplantation. 2008 Nov 15;86(9):1199–205

2 Grenda R, Watson A, Vondrak K, et al. A prospective, randomized, multicenter trial of tacrolimus-based therapy with or without basiliximab in pediatric renal transplantation. Am J Transplant. 2006;6(7):1666–72

3 Höcker B, Kovarik JM, Daniel V, et al. Pharmacokinetics and immunodynamics of basiliximab in pediatric renal transplant recipients on mycophenolate mofetil comedication. Transplantation. 2008;86(9):1234–40.

4 Offner G, Tönshoff B, Höcker B, et al. Efficacy and safety of basiliximab in pediatric renal transplant patients receiving cyclosporine, mycophenolate mofetil, and steroids. Transplantation. 2008;86(9):1241–8.

5 National Institute for Health Care Excellence. Immunosuppressive therapy for kidney transplantation in children and adolescents (technology appraisal guidance 484); 2017

6 Pape L. State-of-the-art immunosuppression protocols for pediatric renal transplant recipients. Pediatr Nephrol. 2019;34(2):187–194.

7 Tönshoff B, Becker JU, Pape L. Nierentransplantation, pp. 243–74. In: Nierenerkrankungen im Kindes- und Jugendalter, Dötsch J, Weber LT (Hrsg.), Springer Berlin, 2024

8 Tönshoff B. Immunosuppressive therapy post-transplantation in children: what the clinician needs to know. Expert Rev of Clin Immunol 2020;16:139–154.

9 Tönshoff B. Immunosuppressants in Organ Transplantation. In: Handbook of Experimental Pharmacology, S. 441–469, Kiess W, Schwab M, van den Anker J (Eds.), Springer Berlin, 2020