# The development of graft-*versus*-host disease prophylaxis

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*https://doi.org/10.3324/haematol.2023.282699*



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| **TITLE** | Methotrexate and cyclosporine compared with cyclosporine alone for prophylaxis of acute graft *versus* host disease after marrow transplantation for leukemia. |
| **AUTHORS** | Storb R, Deeg HJ, Whitehead J, et al. |
| **JOURNAL** | The New England Journal of Medicine 1986;314(12):729-735. PMID: 3513012 |

Allogeneic transplantation is routinely employed as curative therapy for patients with hematologic malignancies and, increasingly, for a variety of non-malignant diseases. Overcoming the barrier of alloimmunity is fundamental to the success of allogeneic transplantation. Thus, the development of potent immunosuppressive medications was the key event leading to the routine use of transplantation for the treatment of hematologic malignancies. Methotrexate was the first widely used immunosuppressive agent, and the development of cyclosporine A in the early

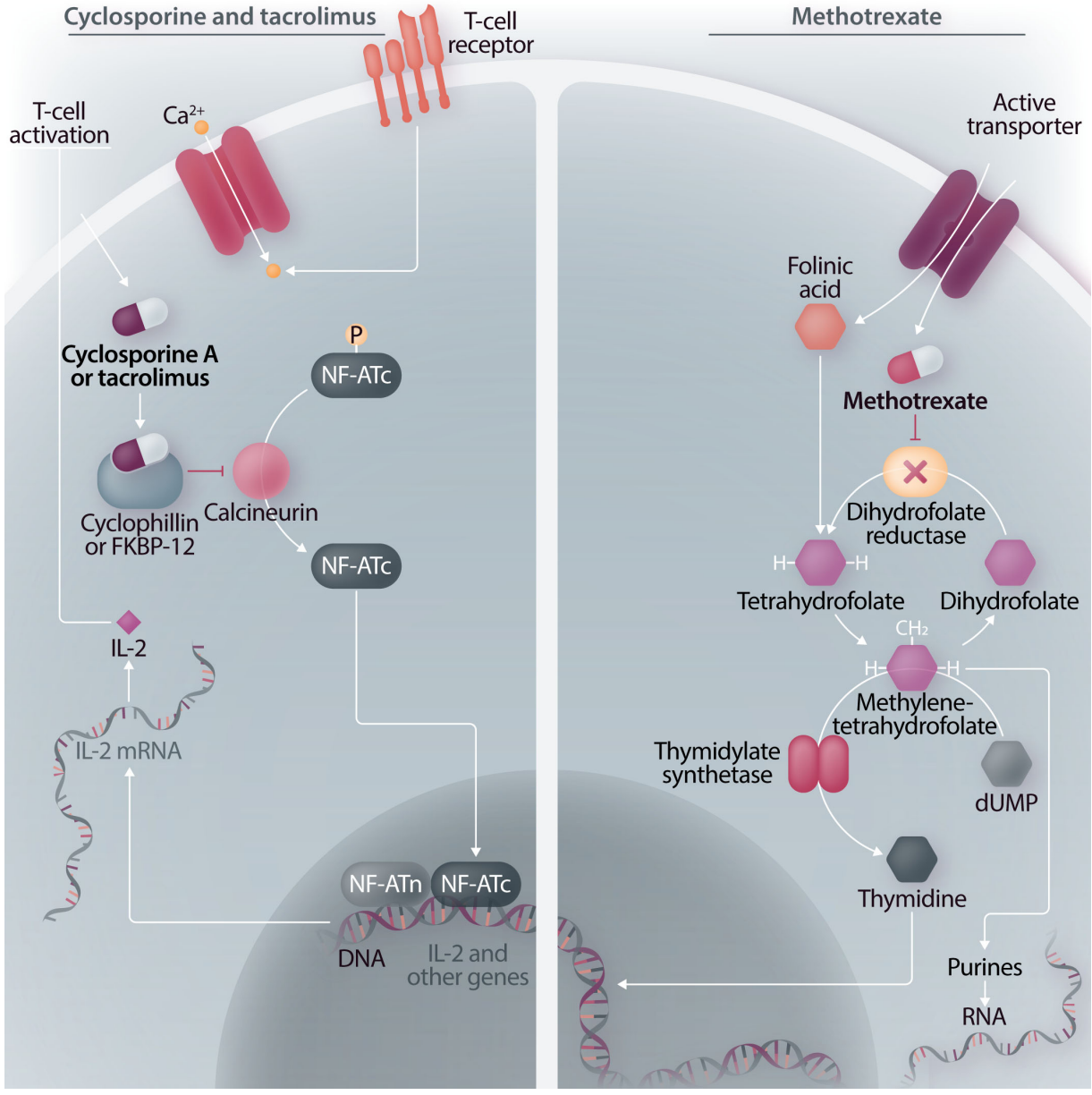


**Figure 1. Mechanisms of action of drugs used in graft-*versus*-host disease prophylaxis.** NF-AT: nuclear factor of activated T cells; IL: interleukin.

1970s represented a major breakthrough in immunosuppression. Methotrexate acts as an antiproliferative agent, preventing cell cycling and division of activated T cells, while cyclosporine A acts by preventing T-cell activation and upregulation in response to inflammatory cytokines and paracrine T-cell signaling. Used individually, each provides some degree of protection against lethal acute graft-*versus*-host disease (GvHD), although single-agent methotrexate is associated with very modest success. Cyclosporine was noted to be more potent as post-transplant monotherapy when compared with methotrexate, leading ultimately to the clinical trial described below.

The landmark randomized trial presented here evaluated the combination of cyclosporine A with methotrexate in comparison to cyclosporine A alone in 93 subjects with acute or chronic myelogenous leukemia transplanted using bone marrow from serologically HLA-matched sibling donors at the Fred Hutchinson Cancer Research Center. This trial,[1] along with the later long-term update,[2] demonstrated a significant improvement in the rate of both overall and severe acute GvHD when the combination was used, and it was this combination of agents that ushered in the era of modern transplantation.

The standard-of-care for GvHD prevention for over 25 years has been the combination of a calcineurin inhibitor (either cyclosporine A or, more recently, tacrolimus, which works through a similar mechanism of action) in combination with an antimetabolite (most frequently methotrexate) (Figure 1). Subsequent clinical trials demonstrated some benefit from the addition of a third immunosuppressive agent, but at the cost of excess infectious morbidity, and the substitution of newer immunosuppressive agents was associated with modest benefits at best. As novel immunosuppressive strategies emerge, including the use of additional chemotherapeutic and targeted agents in the peritransplant period, as well as sophisticated methods of graft manipulation, enabling allogeneic stem cell transplantation between mismatched and even haploidentical donor-recipient pairs, it is important to recognize that the simple combination of cyclosporine A and methotrexate was crucial for tens of thousands of patients who underwent successful related and unrelated donor allogeneic stem cell transplantation over the past 25 years.

**Disclosures**

*No conflicts of interest to disclose.*

# References

1. Storb R, Deeg HJ, Whitehead J, et al. Methotrexate and cyclosporine compared with cyclosporine alone for prophylaxis of acute graft versus host disease after marrow transplantation for leukemia. N Engl J Med. 1986;314(12):729-735.

2. Storb R, Deeg HJ, Pepe M, et al. Methotrexate and cyclosporine versus cyclosporine alone for prophylaxis of graft-versus-host disease in patients given HLA-identical marrow grafts for leukemia: long-term follow-up of a controlled trial. Blood. 1989;73(6):1729-1734.