IMMUNOSUPPRESIVE AGENTS USED IN ORGAN TRANSPLANTATION

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Introduction. In recent decades, organ transplantation has become increasingly accessible for saving patients' lives, and the development of immunosuppressive drugs has played a key role in improving postoperative care, patient survival and quality of life. In this context, efforts are needed to broaden the spectrum of immunosuppressive drugs used for induction and maintenance therapy based on advances in immunology and better understanding of their mechanism of action.
Materials and methods. A selection and analysis of articles published in the PubMed database over the last 10 years was performed in order to elucidate the groups of immunosuppressants, their mechanisms of action and their impact on the immune system.
Results. The main classes of immunosuppressive agents used in organ transplantion include: the calcineurin inhibitors (CNIs-cyclosporine and tacrolimus); mammalian target of rapamycin (mTORi-sirolimus, everolimus); antiproliferative or antimetabolite agents (azathioprine, mycophenolate mofetil); glucocorticosteroids (GC-prednisolone, methylprednisolone); biological immunosuppressive drugs (basiliximab, alentuzumab, rituximab, eculizumab, tocilizumab etc.). Calcineurin inhibitors bind to intracellular proteins (immunophilins), leading to the inhibition of calcineurin and gene transcription in the nuclear factor of activated T-cells pathway in a wide range of cells, including T cells, B cells and all myeloid lineage cells. Mammalian target of rapamycin inhibitors form a complex with the intracellular protein and inhibit the activation of mTOR serine-threonine kinase. This disruption of the IL-2 receptor signaling pathway impairs the proliferation of B and T lymphocytes. Mycophenolate inhibits inosine monophosphate dehydrogenase which results in impaired purine synthesis with broad effects on T cells, B cells, dendritic cells, monocytes, and macrophages. Azathioprine is metabolized to 6-methyl-MP and 6-thioguanine that inhibits DNA synthesis, impairing B- and T-cell proliferation. Glucocorticoids interact with intracellular specific receptors and alter gene regulation leading to changes in cell function, indirect effects via alterations of cytokine release and cell signalling. Belatacept is a fusion protein composed of a modified extracellular domain of the cytotoxic T-lymphocyte antigen 4 and selectively inhibits T-cell activation. Basiliximab, IL-2 receptor monoclonal antibody, inhibits IL-2 binding to IL-2 receptor and thus inhibiting IL-2 dependent T-cell proliferation. Alentuzumab, anti-CD52 monoclonal antibody, binds to CD-52 producing antibody dependent lysis of T-cells and B-cells. Rituximab, anti-CD20 monoclonal antibody, binds to CD-20 producing B-cell depletion via a variety of mechanisms including antibody dependent cytotoxicity and antibody-dependent cellular cytotoxicity. Eculizumab, anti-complement (C5) monoclonal antibody, prevents cleavage of C5 into C5a and C5b and prevents formation of membrane attack complex. Tocilizumab, IL-6 receptor antagonist, inhibits the action of cytokine IL-6.
Conclusions. The analysis showed that most immunosuppressive agents markedly inhibit cellular immunity (T-cells), while humoral immunity was most strongly afected by GC and rituximab, followed by CNIs, antimetabolites, alemtuzumab. In contrast, mTORi and IL-6 receptor antagonists exerted minimal effect on humoral immunity. Innate immunity was effectively diminished by GC and eculizumab.
Keywords: organ transplant, immunosuppressive agents, mechanism of action, cellular immunity, humoral immunity.