Corticosteroids – Azathioprine

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Fifteen years ago, classical immunosuppressive therapy was inconceivable without corticosteroids and azathioprine. A large number of transplantees administering these drugs had successful immunosuppression and good function of the graft over longer period of time. Nevertheless, side-effects of corticosteroids to cardiovascular system (hypertension, congestive heart failure, thrombophlebitis), to endocrine system (iatrogenic Cushing's syndrome, steroid diabetes, hirsutism), osteoarticular system (aseptic necrosis of femoral and humeral head), digestive system and others, contribute to considerable morbidity of these patients. For this reason, the attempts have been made to reduce corticoid doses or even to discontinue their application.

Corticosteroid discontinuation leads to decrease of systolic and diastolic blood pressure, and, accordingly, antihypertensive administration may be interrupted in 15% of patients. Likewise, total cholesterol, LDL cholesterol and triglyceride levels, as well as insulin and oral hypoglycemics requirements are diminished. The growth becomes improved in children with transplants administering immunosuppressive therapy without corticosteroids.

When decision is made to cease corticosteroid therapy, a good selection of patients is required. The allograft function should be stable (with serum creatinine less than 2.5 mg/dl), while the acute rejection of the graft should not happen within at least 6 months before the decision on corticosteroid discontinuation. Corticosteroids should be discontinued gradually during the period of 3-4 months.

Significant is the fact that cadaveric transplantation is used in most countries, and it accounts for 93% of all kidney transplantations in Europe. Data from our country are considerably different: in 1997, out of total number of patients with end-stage CRF, 85% were treated by repeated hemodialysis, 6% by peritoneal dialysis, while only 9% lived with transplanted kidney. On the other hand, out of all transplantations performed up to these days, the graft was received from live donor in even 65% of cases (2), all of them suggesting that this complex medical and organizational problem should be further addressed and solved.

Mode of corticosteroid action

Corticosteroids inhibit T-cell proliferation, T cell-mediated immunity and transcription of cytokine genes (1). Their effects are mostly achieved via blockade of antigen presenting cell (APC) and its production of cytokines (1) and receptors of T lymphocyte co-stimulating activation factors (B7-1 molecule) to APC (2).

Corticosteroids as hydrophobic molecules pass through cell membrane and bind to cytoplasmic receptor (GR). GR is a molecule of 90 kDa, which unbound to steroid, circulates between cytoplasm and nucleus, partially free and partially bound to heat shock proteins (3). Bonding to steroid molecule causes receptor conformation changes (4), receptor dimerization and bonding to specific steroid-sensitive elements (GRE) at the level of nuclear DNA. Receptor dimer reacts with basal transcription factors, leading to gene transcription. Similar effects at DNA level may be achieved by bonding of other receptors (to dopamine or growth factors) to cell membrane through imbalance of kinase and phosphatase (3). Some cytokine genes have affinity for GRE, and therefore, steroid bonding to DNA results in inhibition of transcription of cytokine genes IL-1, IL-2, IL-3, IL-6, TNF-alpha and IFN-gamma (1).

Indirect effects of glucocorticosteroids may produce the reduction of synthesis of chemotactic substances, vasoactive substances, diminished migration of monocytes as well as redistribution of lymphocytes with resulting lymphopenia (1).

Corticosteroids are metabolized by microsomal enzymic system in the liver, and therefore, the drugs affecting this system (phenytoin, barbiturates, rifampicin) may decrease plasma corticosteroid level, while ketoconazole and oral contraceptives increase their plasma concentration (5).

Corticosteroid dosage and application

Medium long-acting corticosteroids are used in kidney transplantation, such as prednisolone and methylprednisolone, and, accordingly a single daily dose as well as low doses of 10 mg/day are sufficient in maintenance therapy, while high and massive corticosteroid doses (15-30 mg7kg) are used in induction and rejection therapies (6). Oral and intravenous drug administration is common (6).

The induction protocol for live, cadaveric and high-risk transplantations prescribes 1.0 g before or during surgery, and 1 mg/kg/BW in postoperative period. Starting from the day 30, the dose is being reduced for 5 mg per week to the dose of 30 mg/day, and thereupon 2.5 mg weekly to the maintenance dose which is usually about 10 mg/day.

The acute rejection is treated by i.v. bolus methylprednisolone in doses of 500 mg on days 1, 2 and 3, 360 mg on day 4, 240 mg on day 5, 120 mg on day 6, 90 mg on day 7, 60 mg on day 8, 40 mg on day 9 and finally by injection of former dose of corticoids on day 10. If there was no re-

sponse to the initial bolus therapy, the patient is given oral prednisolone in doses of 120 mg on days 1, 2 and 3, 90 mg on days 4, 5 and 6, 60 mg on days 7, 8 and 9, 45 mg on days 10, 11 and 12, and finally 30 mg during 8 days with gradual reduction of doses for 5 mg a week (6).

Side-effects of corticosteroids

The administration of corticosteroids is followed by a series of side effects (7) to multiple systems of the body (Table 1).

Table 1 Side-effects of corticosteroids

Organ systems	Side-effects
Water and electrolytes imbalance	Sodium retention, edema, increased ɜotassium and calcium excretion
Cardiovascular system	Hypertension, congestive heart failure, thromboembolism, thrombophlebitis
Muscular-articular system	Muscular pain, fatigue, compression fractures, aseptic necrosis of femoral and humeral head
Gastrointestinal tract	Nausea, vomiting, abdominal distention, peptic ulceration, esophagitis, pancreatitis
Endocrine disorders	Hypercorticism, amenorrhea, and postmenstrual bleeding, diabetes mellitus, hyperglycemia, glucose intolerance, hyperlipidemia
Skin changes	Acne, delayed wound healing, hirsutism, skin atrophy, ecchymosis
Ocular changes	Glaucoma, posterior subcapsular cataract, frequent fungal infection of the eye
Nervous system impairments	headache, vertigo, convulsions, increased motor activity, insomnia, modified temper, psychosis
Other	Higher susceptibility to infection, disguised infection symptoms

Manifestation of side-effects is related to dose and length of administration (7). Accordingly, the treatment goal is to maintain therapeutical drug effects with minimum dosage in addition with other immunosuppressants of lower toxic effects.

Discontinuation of corticosteroids - advantages and disadvantages

In the last few years, several attempts have been made to discontinue completely the corticosteroids in therapeutical protocols (8, 9, 10, 15, 16, 17). Namely, although corticosteroids may produce hypertension (8) along with other factors (recurrence of underlying renal disease, arterial stenosis of transplant, hormonal effect of native kidneys, chronic and acute transplant rejection), it has been reported that discontinuation of corticosteroids gives rise to lower systolic and diastolic blood pressure, reduced antihypertensive doses while the drug administration may be terminated in even 15% of patients (9). In similar number of patients, total cholesterol, LDL cholesterol concentration and triglycerides, need for insulin or oral hypoglycemics are also diminished. The improvement of growth is evident in children transplantees covered by immunosuppression without corticosteroids (9).

Current recommendations stress the significance of careful selection of patients in whom corticosteroids will be discontinued. The allograft function should be stable with serum creatinine level less than 2.5 mg/dl, without the history of acute rejection in at least 6-month period before the decision on corticosteroid discontinuation, while the patients are to be older (10). Corticosteroid therapy should be discontinued gradually during the period of 3-4 months.

Azathioprine

Azathioprine is 1-methyl-4nitro5-imidazolyl derivative of 6-mercaptopurine, i.e. purine analogue acting as purine antagonist.

Mode of action

Azathioprine inhibits the synthesis of purine alkali, preventing the synthesis of RNA, nucleotide metabolism and cell proliferation by bonding to immunophylline (1). It is especially important for myelocytogenesis, particularly of promyelocytes, whose inhibition again inhibits the production of monocytes and APC, and also the expansion of T and B lymphocyte clones (1). Concurrent administration of allopurinol on account of adjunctive effect to blocking of purine and azathioprine catabolism may significantly enhance the suppression of bone marrow (5).

Dosage and application

Following the transplantation, the induction doses of azathioprine ranges from 2 to 3 mg/kg, and they are subsequently reduced to usual 1-2 mg/kg depending upon other protocol immunosuppressants used (6). In oral drug therapy, 50% of administered dose is resorbed, but as azathioprine level is not measured in blood, monitoring of toxic effects of the drug is necessary. If myelotoxicity is manifested, the dose must be reduced, while the application of drug must be interrupted if the white blood cell count is less than $3000/mm^3$ and platelet count is less than $80000/mm^3$ (5).

Some studies have reported significantly lower incidence of the acute rejection with triple conventional therapy using higher doses of azathioprine (13). Yet, some other studies have emphasized that the introduction of micophenolate mophethyl into standard therapy significantly promotes the survival of kidneys and pancreas in combined renal and pancreatic transplantation (14).

Azathioprine is metabolized in 6-thiouric acid by the action of xanthine oxidase (5). Therefore, the inhibition of xanthine oxidase by allopurinol demands the reduction of the initial azathioprine dose for 30-50% in their simultaneous application (6).

Side-effects
Side-effects of azathioprine (5) are illustrated in Table 3.

Table 3. Side-effects of azathioprine

Organ system	Side-effects
Bone marrow	Leukopenia, macrocytic anemia, thrombocytopenia
Gastrointestinal tract	Nausea and vomiting, hepatotoxicity, pancreatitis
Skin	Alopecia
Other	Susceptibility to infections, higher incidence of neoplasms
Drug interaction	Allopurinol

Conclusion
Based on long-term experience of corticosteroid application and azathioprine in kidney transplantation, it is apparent that administration of these drugs, in spite of intensive development of new immunosuppressants, still has a key role in treatment and it will not be withdrawn for some time. Full consideration of side-effects of these drugs, along with careful dosage and clinically controlled introduction of new immunosuppressants, will track the way to new immunosuppressive protocols with significantly better survival of graft and lower morbidity and mortality of patients with kidney transplants.
Up to 1983, when the application of cyclosporin A (CsA) was initiated, 25 kidney transplantations were performed in the Center for kidney transplantation. Since then, 511 kidney transplantations were carried out, out of which 443 (87.3%) patients were covered by triple immunosuppressive therapy: cyclosporine, azathioprine and corticosteroids. Due to cyclosporine nephrotoxicity, triple therapy was converted into azathioprine and corticosteroid therapy in 18 patients. All 18 patients manifested the decrease of serum creatinine level, creatinine clearance, mean systolic and diastolic pressure as well as cholesterol concentration, triglycerides and proteinuria in 24 hours. None of 18 cases had rejection crisis in the first 6 to 12 months.
Out of 525 patients, 274 (52.3%) were found to be at higher immunological risk: evidently higher lymphocyte stimulation index in mixed culture medium, present cytotoxic antibodies over 35% or different but compatible blood groups, or they were candidates for kidney retransplantation.
Out of 274 patients, the rejection crisis in the first 6 months were manifested in 167 (61.7%) patients who were treated by pulse steroid doses yielding good response in patients, what was evident by subsequent recovery of renal function. Both drugs belong to the history of immunosuppressive therapy, but they had their place in the treatment of patients with kidney transplants.

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