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REVIEW

Rational use of immunosuppressive drugs in vasculitis treatment

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ABSTRACT

Immunosuppressive drugs are essential for the treatment of inflammatory and autoimmune diseases, such as vasculitis. A complete understanding of pharmacological profiles, interaction potentials, and patient-specific variables is necessary for rational drug use. Azathioprine, methotrexate, mycophenolate mofetil, cyclophosphamide and glucocorticoids are common immunosuppressants that have complex pharmacokinetics and are linked to a variety of interactions between drugs, nutrients, and supplements, which may increase the toxicity or change the therapeutic response. Their safety and effectiveness are greatly influenced by metabolic polymorphisms, cytochrome P450 enzymes, and P-glycoprotein transporters. Serious side effects such as nephrotoxicity, myelosuppression, or decreased treatment response might result from inappropriate combinations. Therefore, therapeutic drug monitoring and individualization of therapy by a multidisciplinary approach becomes important. This review emphasizes the importance of rational use of these drugs, patient monitoring and management of drug interactions to ensure safe and effective immunosuppressive therapy, while minimizing preventable risks and maximizing patient outcomes.

Keywords: Rational drug use, immunosuppressives, drug interactions, pharmacist.

INTRODUCTION

Vasculitis refers to a heterogeneous group of rare disorders characterized by inflammation and necrosis of blood vessel walls, which can lead to tissue ischemia and organ dysfunction. The overall prevalence depends on the subtype and geographic region [1]. Although etiology-based disease classification is frequently the preferable method, most vasculitides cannot be classified in this way since the etiology is unclear [2]. Timely diagnosis and initiation of immunosuppressive therapy are critical for improving outcomes and preventing irreversible organ injury, as highlighted by the EULAR recommendations for the management of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis [3-5].

The pathophysiology of vasculitis and inflammatory processes are actively influenced by the endothelial injury through mechanisms, such as abnormal T-cell activation, autoantibody production (e.g., ANCA), and pro-inflammatory cytokine release [e.g., Tumour Necrosis Factor (TNF)-α, Interleukin (IL)-6] [6]. Immunosuppressive drugs target these pathways at different levels: calcineurin inhibitors (e.g., tacrolimus, cyclosporine) inhibit T-cell activation by blocking IL-2 transcription; mycophenolate mofetil suppresses lymphocyte proliferation via inosine monophosphate dehydrogenase inhibition; azathioprine interferes with purine synthesis; methotrexate inhibits dihydrofolate reductase, reducing pro-inflammatory immune cell turnover and cyclophosphamide is an alkylating agent that prevents cell division by cross-linking DNA strands and decreasing DNA synthesis and exerts its immunomodulatory effect via T cells regulations and rituximab, as a monoclonal antibody, suppresses the immune response by targeting the

CD20 receptor on the surface of B lymphocytes. Glucocorticoids suppress the immune response mainly by reducing the production of pro-inflammatory cytokines and limiting the movement of white blood cells to sites of inflammation. As these drugs exert immunosuppressive effects through distinct pathways, significant interindividual variability, and potential drug–drug and drug–nutrient interactions, their use requires careful consideration to balance efficacy and safety [2, 7, 8].

Treatment Strategy

The complex classification systems and largely unknown etiologies of vasculitides have complicated disease management; nevertheless, treatment strategies have continued to evolve with the use of various immunosuppressive drugs and the introduction of novel approaches, including biologic therapies. When administered with or without immunosuppressive medications, glucocorticoids are the first-line treatment for individuals with vasculitis. The selection of immunosuppressive medications is based on the type of vasculitis [9]. Among the different types of vasculitis, ANCA-associated vasculitis is considered the one that most clearly requires immunosuppressive treatment. It is followed by conditions such as Giant Cell Arteritis (GCA), Polyarteritis Nodosa (PAN), Takayasu Arteritis (TAK), Immunoglobulin (Ig) A vasculitis, and cryoglobulinemic vasculitis [4, 5, 10-12].

Treatments for various types of vasculitis have included the use of methotrexate (MTX), azathioprine (AZA), mycophenolate mofetil (MMF), cyclophosphamide (CYC), rituximab (RTX), intravenous immunoglobulin, plasma exchange, and others [6]. It is imperative to determine the most appropriate immunosuppressive treatment for each patient, with the objective of enhancing treatment outcomes while mitigating the risk of adverse effects. Since these drugs are widely used and often involve complex regimens, a clear understanding of potential drug interactions and implementation of principles of rational drug usage is inevitable [13].

Rational Use of Immunosuppressive Drugs

The rational use of immunosuppressive drugs aims to achieve optimal therapeutic outcomes by ensuring appropriate indications, dosing, and treatment duration. These drugs are primarily employed in managing serious conditions such as vasculitis, organ transplantation, and autoimmune diseases. However, due to their immunosuppressive effect, they have risks of severe complications, including infections, malignancies, and organ toxicities. Therefore, comprehensive assessment of individual factors (such as comorbidities, age, renal and hepatic function, immune status, and medication adherence), consideration of indications, management of drug interactions, and close monitoring of treatment response are critical components of their rational use [4, 5, 7]. For example; elderly patients have an increased risk of hematologic toxicity with drugs like MMF, while AZA metabolism may be impaired in those with hepatic insufficiency [14, 15].

Therapeutic drug monitoring (TDM) is a strategy employed to ensure the rational use of immunosuppressive drugs, however, it is commonly used for calcineurin inhibitors such as tacrolimus and cyclosporine. Mycophenolate mofetil and azathioprine do not have widely established TDM protocols, but measurement of mycophenolic acid levels or metabolites may be considered in selected cases [8]. Drug information leaflets, clinical guidelines, and patient-specific pharmacokinetic calculations support the evidence-based dose adjustments.

Glucocorticoids remain the mainstay of rational immunosuppressive therapy in vasculitis due to their potent and rapid anti-inflammatory effects. When administered at immunosuppressive doses that are tailored to the severity of the disease, it enables effective control of vascular inflammation. Nevertheless, given their substantial side effect profile, particularly in cases of long-term, high-dose usage, meticulous dose optimization, gradual tapering and close monitoring of signs and symptoms are paramount to ensure their judicious utilization [10, 12].

Risk of Drug Interactions

Immunosuppressive drugs are susceptible to a range of pharmacological interactions. The most immunosuppressive drugs have the potential to interact through hepatic metabolism [mainly via cytochrome P450 (CYP) enzymes], renal elimination, and modulation of the immune system [13, 16].

Drug interactions are generally classified into two main categories: pharmacokinetic and pharmacodynamic. Pharmacokinetic interactions result from alterations in the absorption, distribution, metabolism, or excretion pathways of a drug once concomitantly used with the other. Concomitant administration of medications can result in interactions that influence the plasma levels of each drug, potentially leading to sub-therapeutic (inefficacy) or supra-therapeutic (toxicity) levels of either or both medications. For example, the absorption of mycophenolate mofetil can be impaired with antibiotics such as cephalosporins or rifampin, which leads to decreased plasma levels. Cyclosporine, mycophenolate mofetil and cyclophosphamide are metabolized via the CYP enzymes and P-glycoprotein system; therefore, the plasma concentrations can reach the toxic levels when co-administered with azole antifungals, calcium channel blockers, or macrolide antibiotics [8, 17, 18]. On the other hand, pharmacodynamic interactions involve the direct or indirect enhancement or reduction of drug effects at the site of action, which occur as additive, synergistic or antagonist mechanisms. For instance, concurrent use of methotrexate and nonsteroidal anti-inflammatory drugs (NSAIDs) may accelerate impairment of renal function, thereby increasing methotrexate toxicity. Similarly, a combination of azathioprine with myelotoxic drugs, such as co-trimoxazole or allopurinol increases the risk of pancytopenia [19]. Such interactions are particularly critical in serious conditions like vasculitis, where they can disrupt the balance between therapeutic efficacy and toxicity; therefore, close clinical monitoring (including therapeutic drug monitoring) and avoidance of drugs with interaction risk (where appropriate) are essential. Azathioprine is metabolized via the xanthine oxidase enzyme; therefore, concomitant use with xanthine oxidase inhibitors such as allopurinol significantly increases 6-mercaptopurine levels, markedly increasing the risk of bone marrow suppression. If this combination is unavoidable, the azathioprine dose should be reduced by 25–50%, and hematological parameters must be closely monitored [19]. Mycophenolic acid, the active metabolite of MMF, undergoes enterohepatic recirculation; consequently, antibiotics such as rifampin, ciprofloxacin, and amoxicillin-clavulanate have the potential to reduce the levels of mycophenolate, thereby diminishing its therapeutic efficacy. Therefore, it is crucial that antibiotic preferences are given particular consideration in patients at risk of sepsis during vasculitis flare-ups [20]. Methotrexate is eliminated primarily via renal tubular secretion. Concomitant drugs such as, NSAIDs, proton pump inhibitors (PPIs) like omeprazole and lansoprazole, and trimethoprim can reduce methotrexate (particularly with high-dose) clearance and increase the risk of toxicity, including hepatotoxicity and bone marrow suppression. When such combinations are required, using lower doses and close monitoring is recommended. Similarly, the risk of adverse effects of cyclophosphamide may increase by concomitant use of allopurinol, antifungals, barbiturates, linezolid and thiazide diuretics [21]. Since the metabolism of rituximab is mainly by various proteases and its elimination is mediated by the reticuloendothelial system, there are limited drug interactions when administered concomitantly, with the exception of concurrent use with cidofovir and talimogene laherparepvec, which are absolute contraindications [22]. However, as is applicable to all immunosuppressive drugs, co-medication with other immunosuppressives may enhance this effect and lead to pronounced myelosuppression.

Pharmaceutical incompatibility refers to drug stability and incompatibilities, which indicates the formation of precipitates or acid-base reactions resulting from physicochemical changes associated with the administration of certain parenteral drugs or mixtures together. In contrast to pharmacokinetic and pharmacodynamic interactions, drug incompatibilities occur prior to the drugs entering the body and can arise between drugs, drugs and solvent solutions, drugs and infusion system materials, or medical devices [23]. Therefore, a clear distinction should be made between the terms of drug stability, incompatibilities and drug interactions when using drugs concomitantly.

Not only with the drugs, but also certain foods may affect the outcome of drug treatment [24]. Antiproliferative drugs such as MMF can also interact with nutrients; its absorption may be delayed by high-fat meals; however, its overall bioavailability is not significantly affected. In contrast, the enteric-coated form, mycophenolate sodium, is generally preferred to be taken after meals. Additionally, supplements containing aluminum and magnesium (e.g., antacids) may

impair the absorption of MMF [25]. High-dose folic acid supplementation during methotrexate therapy may reduce the drug's efficacy; therefore, folic acid supplementation should be carefully planned with respect to dose and timing specific to the treatment regimen [26].

Furthermore, the efficacy and safety of immunosuppressive drugs may be affected by herbal supplements. It is well-known that St. John's Wort (*Hypericum perforatum*) is a potent CYP3A4 inducer, which may decrease the level of cyclosporine or glucocorticoids. Supplements includes Ginseng (*Panax ginseng*) or *Echinacea (Echinacea purpurea)* have been observed to stimulate the immune system, thereby reducing the effectiveness of drugs such as azathioprine, mycophenolate mofetil, and tacrolimus. Additionally, ginseng may affect their metabolism via CYP3A4 and P-glycoprotein [27].

Although commonly used interaction checker programs offer a helpful insight in identifying potential drug interactions, their clinical relevance, especially in patients receiving immunosuppressive therapy often requires careful interpretation. For drugs with a narrow therapeutic index, such as tacrolimus or cyclosporine, even minor changes in metabolism can lead to significant toxicity or treatment failure. This is where clinical pharmacists take an active role by not just recognizing interactions, also by evaluating their clinical significance and real impact on the treatment outcomes and consequently help to maintain safe and effective drug treatment [28].

CONCLUSION

The rational use of immunosuppressive drugs demands a collaborative approach, aimed at achieving a balance between adequate immunosuppression and the minimization of adverse effects. Therapeutic drug monitoring, individualized patient assessment of (e.g., age, organ function, comorbidities, antigen-related factors), and adherence to clinical guidelines are all practices undertaken to ensure safety and efficacy. It is therefore vital to emphasize the importance of multidisciplinary collaboration, increased vigilance among healthcare providers, and patient education regarding self-use of supplements in order to improve outcomes and reduce the incidence of preventable complications associated with immunosuppressive drugs.

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