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VIEW AND REVIEW

Immunosuppressors and immunomodulators in Neurology – Part I: a guide for management of patients under immunotherapy

Imunossupressores e imunomoduladores em Neurologia – Parte I: um guia para o manejo de pacientes em imunoterapia

Fabiano Ferreira ABRANTES[1], Marianna Pinheiro Moraes de MORAES[1], José Marcos Vieira de Albuquerque FILHO[1], Jéssica Monique Dias ALENCAR[1], Alexandre Bussinger LOPES[1], Wladimir Bocca Vieira de Rezende PINTO[1], Paulo Victor Sgobbi de SOUZA[1], Enedina Maria Lobato de OLIVEIRA[1], Acary de Souza Bulle de OLIVEIRA[1], José Luiz PEDROSO[1], Orlando Graziani Povoas BARSOTTINI[1]

ABSTRACT

For patients with autoimmune diseases, the risks and benefits of immunosuppressive or immunomodulatory treatment are a matter of continual concern. Knowledge of the follow-up routine for each drug is crucial, in order to attain better outcomes and avoid new disease activity or occurrence of adverse effects. To achieve control of autoimmune diseases, immunosuppressive and immunomodulatory drugs act on different pathways of the immune response. Knowledge of the mechanisms of action of these drugs and their recommended doses, adverse reactions and risks of infection and malignancy is essential for safe treatment. Each drug has a specific safety profile, and management should be adapted for different circumstances during the treatment. Primary prophylaxis for opportunistic infections and vaccination are indispensable steps during the treatment plan, given that these prevent potential severe infectious complications. General neurologists frequently prescribe immunosuppressive and immunomodulatory drugs, and awareness of the characteristics of each drug is crucial for treatment success. Implementation of a routine before, during and after use of these drugs avoids treatment-related complications and enables superior disease control.

Keywords: Immunosuppressive Agents; Immunologic Factors; Adrenal Cortex Hormones; Multiple Sclerosis; Autoimmune Diseases; Neurology.

RESUMO

Pacientes com doenças autoimunes exigem uma constante preocupação com os riscos e benefícios do tratamento imunossupressor ou imunomodulador. O conhecimento das rotinas no uso de cada uma dessas drogas é fundamental para o bom desfecho clínico, evitando a piora da doença ou efeitos colaterais. As drogas imunossupressoras e imunomoduladoras agem em diferentes pontos da resposta imunológica a fim de controlar a doença para qual são indicadas. O conhecimento do mecanismo de ação, principais posologias, efeitos adversos e os riscos de infecções e neoplasias relacionadas ao uso dessas medicações são fundamentais para um tratamento seguro. Cada uma delas apresenta um perfil específico de complicações e o manejo deve ser individualizado em diferentes cenários ao longo do seguimento do paciente. O uso de medicações para profilaxia primária de infecções e a vacinação são pontos essenciais no planejamento do tratamento, prevenindo potenciais complicações infecciosas ao longo do acompanhamento. O uso de imunossupressores e imunomoduladores é uma frequente realidade no dia-a-dia do neurologista, e o conhecimento das características de cada droga é crucial para o sucesso do tratamento. A realização de uma rotina antes, durante e depois do uso dessas medicações evita complicações relacionadas com o tratamento e alcança um melhor controle da doença.

Palavras-chave: Imunossupressores; Fatores Imunológicos; Corticosteroides; Esclerose Múltipla; Doenças Autoimunes; Neurologia.

[1]Universidade Federal de São Paulo, Departamento de Neurologia, Divisão de Neurologia Geral, São Paulo SP, Brazil.

FFA https://orcid.org/0000-0002-3813-5993; MPMM https://orcid.org/0000-0003-1273-9083; JMVAF https://orcid.org/0000-0002-4533-2637; JMDA https://orcid.org/0000-0002-6354-4043; ABL https://orcid.org/0000-0001-5466-2155; WBVRP https://orcid.org/0000-0002-0150-525X; PVSS https://orcid.org/0000-0002-7416-7108; EMLO https://orcid.org/0000-0002-4939-7200; ASBO https://orcid.org/0000-0002-6986-4937; JLP https://orcid.org/0000-0002-1672-8894; OGPB https://orcid.org/0000-0002-0107-0831

Correspondence: Fabiano Ferreira Abrantes; Email: fabianofabrantes@hotmail.com.

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INTRODUCTION

Significant developments within Immunology over the last decades have led to marked improvement in diagnosis and management of autoimmune disorders. A close relationship between Neurology and Immunology has been demonstrated by the large number of neurological disorders for which the pathophysiological explanation relates to immune-mediated mechanisms. Discoveries of new autoantibodies and new therapies have been increasing.

Considering all the developments at the interface of Neurology and Immunology, Autoimmune Neurology has been emerging as a new subspecialty[1]. In order to improve knowledge of and care for patients with autoimmune and demyelinating disorders, there is a large need for updates on management of these disorders. In line with this, drug management of autoimmune disorders requires understanding of accurate drug dosing, infusion schedules and the most suitable infection screening and follow-up.

We searched the PubMed and Scientific Electronic Library Online (SciELO) databases for published studies in Portuguese and English over the period 1990–2020. Through the search process, articles that described drug pharmacology, administration schemes, adverse effects and other safety issues were included. Articles and guidelines describing the major points relating to opportunistic infections and vaccination in patients under immunosuppression or immunomodulation were also included. The aim of this review of the literature was to provide a practical approach and guidance for general neurologists with regard to drug management for patients with different forms of autoimmune disorders that affect the nervous system.

IMMUNOSUPPRESSIVE AND IMMUNOMODULATORY DRUGS

Several types of immunosuppressive drugs are commonly used for patients with immune-mediated neurological disorders, and the most commonly used types within daily practice are discussed in the following topics and are summarized in Table 1.

CORTICOSTEROIDS

Corticosteroids are synthetic hormones that mimic the action of endogenous cortisone and modify metabolism and immune function through protein expression at DNA level. Also, corticosteroids reduce inflammatory responses and decrease lymphocyte, eosinophil and basophil counts[2].

Prednisone is four times as potent as hydrocortisone. The usual dose of prednisone for immunosuppressive effects is 30 mg per day[3]. Other corticosteroids include dexamethasone, methylprednisolone and deflazacort. Table 2 summarizes the relative activity and length of action of different corticosteroids.

Corticosteroids are used for a variety of different neurological conditions, and not only autoimmune disorders: inflammatory processes relating to infections (e.g., tuberculosis or bacterial meningitis), primary refractory headaches (e.g., cluster headache), Duchenne muscular dystrophy and autoimmune or autoinflammatory diseases (e.g. Behçet's syndrome, Still's disease, sarcoidosis, multiple sclerosis relapses, neuromyelitis optica spectrum disorder [NMOSD] relapses, acute disseminated encephalomyelitis [ADEM], etc.).

Side effects relating to use of corticosteroids are common, and include insomnia and mood changes (euphoria); increased risk of sepsis; venous thromboembolism; bone fractures; obesity; glucose intolerance; diabetes; myopathy; osteoporosis; peptic ulcer; skin lesions; and infections[4,5].

Pulse therapy is defined as treatment with doses higher than 250 mg of prednisone or its equivalent[6]. Methylprednisolone is more widely used than prednisone for pulse therapy because of its lower mineralocorticoid activity. Pulse therapy with dexamethasone has shown similar results in patients with MS and optic neuritis[7]. The usual dose of methylprednisolone is 1 g administered as an infusion diluted with 0.9% saline solution over 1-3 hours (to avoid hemodynamic instability) for 3 to 5 days. Before starting to administer pulse therapy, it is recommended that an evaluation should be conducted through routine laboratory tests (glucose, urea, creatinine and blood count), with prophylaxis for disseminated strongyloidiasis using antiparasitic drugs (e.g. ivermectin at 200 mcg/kg). During drug infusion, vital sign monitoring is essential. Long-term corticosteroid use requires gradual tapering to avoid hypothalamic-pituitary-adrenal axis suppression. For short-term use (less than 14 to 21 days) (including pulse therapy schemes), this tapering is not necessary[8].

An initial metabolic profile, including screening for diabetes, dyslipidemia and vitamin D levels, should be assessed prior to starting administration of corticosteroid. Table 3 shows the basic monitoring during treatment with corticosteroids.

Corticosteroid-induced osteoporosis is usually multifactorial[5]. Assessment of bone mineral density (BMD) is required before treatment and within one year. If BMD remains stable, this assessment can be repeated within 2-3 years[3]. Both calcium and vitamin D supplementation is recommended, in order to prevent BMD reduction[9]. The Fracture Risk Assessment Tool (FRAX) is a tool for evaluating patients' risk of fractures and it can help in deciding when to start treatment with common bisphosphonates[10]. Hip pain needs to be assessed by means of x-rays and/or magnetic resonance imaging (MRI) because of the risk of spontaneous osteonecrosis. Patients on high-dose GLC should be evaluated for ophthalmological complications (e.g. glaucoma and cataracts) after an interval of 6-12 months.

One practical approach for corticosteroid dosage reduction to prevent serious side effects is to reduce the dose by 10-20% every 2-4 days. After reaching a dose of 5 mg of prednisone or equivalent, the adrenal axis should be tested (serum ACTH and morning cortisol levels). If test results are normal, corticosteroids can be discontinued[11]. We recommend that patients with abnormal test results should be referred to an endocrinologist

Table 1. Main immunosuppressive and immunomodulatory drugs used in Neurology.

Drug	Dose	Special issues	Interactions	Follow-up	Pregnancy and breastfeeding
Azathioprine (AZA)	Initial: 50 mg/day Dose increase: 25-50 mg/week or two weeks Aimed dose: 2-3 mg/kg/day	Extremes of weight, old age, hepatic insufficiency and renal insufficiency give rise to higher risk of toxicity Low levels of TPMT: increased risk of myelosuppression	Xanthine oxidase inhibitors increases toxicity (e.g. allopurinol) ACEi increases the chance of leukopenia AZA reduces warfarin effect	CBC, Cr, AST, ALT on starting and weekly after dose changes, until stable dose is reached; and then every 12 weeks thereafter	Can continue to be given during pregnancy but should not be started during it. Safe in breastfeeding.
Methotrexate (MTX)	Initial: 7.5-15 mg/day Dose increase: 5-10 mg per 2 weeks or 4 weeks Aimed dose: 20-25 mg/day	Supplementation of folic acid 5 mg one day after MTX administration	Other drugs that deplete folate (e.g. sulfamethoxazole-trimethoprim) increase myelosuppression risk	CBC, Cr, AST, ALT on starting and weekly after dose changes, until stable dose is reached; and then every 12 weeks thereafter	Contraindicated during pregnancy and lactation
Mycophenolate mofetil (MMF)	Initial: 500 mg daily for several days Target dose: 1.5 and 3 grams divided twice daily	Do not exceed 2 grams daily if GFR < 25 ml/min	Proton pump inhibitors can decrease MMF absorption. Rifampin decrease MMF serum concentration and acyclovir can increase it. MMF may decrease serum concentrations of hormonal contraceptives (pills, patches and vaginal rings)	Prior to MMF therapy: CBC, liver function tests, Cr, urinalysis, serological tests for HBV and HCV, screening for latent tuberculosis (TST or IGRA). New CBC 1-2 weeks after the start of therapy and if no evidence of bone marrow suppression, check every 6-8 weeks	Contraindicated during pregnancy and lactation
Cyclosporin	Initial dose: 2.5 mg/kg every 12 hours Adjustment of dose according to serum level, to achieve 100-150 mcg/liter	Increased risk of lymphoproliferative disorders	Selective serotonin reuptake inhibitors, statins, azole antifungals, non-dihydropyridine calcium channel blockers and angiotensin receptor blockers raise cyclosporin level Rifampicin, carbamazepine, phenytoin and phenobarbital decrease cyclosporin level	Serum cyclosporin electrolytes, Cr, AST, ALT, coagulation tests, hemolysis biomarkers Annual dermatoscopic evaluation	This should be given during pregnancy if the benefits outweigh the risks Breastfeeding is contraindicated
Cyclophosphamide (CYP)	Initial: 500-750 mg/m^2 every 4 weeks Dose adjustment: According to leukocyte nadir (7th-14th day of infusion). Less than 3500 leukocytes or less than 1500 neutrophils reduces the next dose by 20-25%. If leukocytes are higher than 4000, consider an increase of 20-25% at the next dose.	Attention regarding hydration on the day of the infusion. Consider mesna in children and patients with cardiopathy or nephropathy. Higher doses increase chances of cancer (leukemia, bladder and skin cancer). Male and female infertility (risk increases with an accumulated dose higher than 10 g). Dose adjusted with GFR < 10 ml/min.	Ondansetron, clopidogrel, paroxetine and sertraline could reduce the CYP effect. Phenytoin, carbamazepine and rifampicin could increase the toxicity.	CBC, Cr, AST, ALT and urinalysis monthly (7th-14th day after the infusion)	Contraindicated during pregnancy and lactation
Infliximab	IV 3-7 mg/kg at 0, 2 and 6 weeks, with maintenance infusions every 4 to 8 weeks.	In heart failure, individualize risk and benefit: NYHA Class I/II no adjustment necessary, monitor closely; NYHA Class III or IV: ↓ 5 mg/kg. No renal adjustment. If hepatotoxicity during treatment (jaundice and/or increase in liver enzymes (↑ 5 times ULN), discontinue treatment. Consider antihistamines, acetaminophen and/or corticosteroids to prevent infusion-related reactions. Caution in patients with history of seizures.	Enhances the risk of T-cell non-Hodgkin's lymphoma and increases serum concentration of active metabolite when used with azathioprine.	Active and latent TB screening prior and during therapy; HBV screening prior to initiating (all) and during and for several months after therapy (HBV carriers); AST, ALT. Attention for signs and symptoms of malignancy (hepatosplenomegaly, persistent fever, weight loss)	Live vaccines should be avoided for the first 6 months of life if the exposure occurs after the 1st trimester of pregnancy. Compatible with breastfeeding but should be discussed (potential transfer into breast milk 2-3 days after dose).

Table 1. Cont.

Drug	Dose	Special issues	Interactions	Follow-up	Pregnancy and breastfeeding
Adalimumab	40 mg every other week subcutaneously	No dosage adjustments for renal or hepatic impairment. No dose particularity for geriatric patients. No contraindications reported.	Concurrent use with azathioprine, methotrexate and prednisone increases risk of serious infection.	Active and latent TB screening prior to and during therapy; HBV screening prior to initiating (all) and during and for several months after therapy (HBV carriers); AST, ALT. Attention for signs and symptoms of malignancy (hepatosplenomegaly, persistent fever, weight loss)	Live vaccines should be avoided for the first 6 months of life if the exposure occurs after the 1st trimester of pregnancy. Compatible with breastfeeding but should be discussed (potential transfer into breast milk 2-3 days after dose).
Rituximab	375 m^2/week for 4 consecutive weeks 1000 mg on day 1 and day 15 Premedication with 100 mg of methylprednisolone is recommended before every infusion	Consider Ig reposition if the patient presents with recurrent infections and IgG levels lower than 6 g/L.	Anti-neoplastic, immunomodulatory and immunosuppressive drugs.	CBC, CD19+ assays (4-6 weeks), IgG, IgA and IgG levels (at beginning and if recurrent infections occur) Active and latent TB screening prior and during therapy; HBV screening prior to initiating; Malignancy screening.	Contraindicated during pregnancy. Compatible with breastfeeding but should be discussed (potential transfer into breast milk 2-3 days after dose).
Ocrelizumab	300 mg, IV, on days 1 and 15. 600 mg, IV, every 6 months at the following doses. Premedication with 100 mg of methylprednisolone is recommended before every infusion.	High incidence of herpes virus infections.	Anti-neoplastic, immunomodulatory and immunosuppressive drugs.	CBC, CD19+ assays, IgG, IgA and IgG levels (if recurrent infections) Malignancy screening.	Contraindicated during pregnancy and lactation
Ofatumumab	20 mg, SC, on days 1, 7 and 14, and every 4 weeks after loading doses.	Injection-site reactions	Anti-neoplastic, immunomodulatory and immunosuppressive drugs.	CBC, CD19+ assays, IgG, IgA and IgG levels (if recurrent infections) Malignancy screening.	Contraindicated during pregnancy and lactation
Alemtuzumab	12 mg, IV, 5 days in year 1. 12 mg IV, 3 days in years 2, 3 and 4. The infusion has to be done for 4 hours to prevent infusion-associated reactions, combined with antipyretics, antihistamines and corticosteroids prior to the infusion.	Herpes zoster prophylaxis. Baseline thyroid hormones, platelets, creatinine levels and urine analysis.	Anti-neoplastic, immunomodulatory and immunosuppressive drugs.	CBC, TSH, T4, Cr, urinalysis. Every 3 months and 48 months after the last dose, testing for autoantibodies (anti-GBM, anti-thyroperoxidase, thyrotropin receptor antibodies) must be done.	Contraindicated during pregnancy and lactation
Natalizumab	300 mg, IV, every 4 weeks for 24 weeks, or longer periods in extended interval doses.	PML in JCV-positive patients.	Anti-neoplastic, immunomodulatory and immunosuppressive drugs.	CBC. JCV every 6 months	This should be given during pregnancy if the benefits outweigh the risks Breastfeeding is contraindicated
Cladribine	3.5 mg/kg, orally, via 10 mg tablets, four to five days in weeks 1 and 5 for two subsequent years. Maximal dose: 100 mg.	Total blood count, herpes zoster serology, tuberculosis screening. Vaccines should be updated.	Anti-neoplastic, immunomodulatory and immunosuppressive drugs.	CBC every 6 months	Contraindicated during pregnancy and lactation

Table 1. Cont.

Drug	Dose	Special issues	Interactions	Follow-up	Pregnancy and breastfeeding
Dimethyl fumarate	120 mg orally, twice a day, after 7 days start a maintenance dose of 240 mg orally twice a day.	Administered with food for TGI effects. Aspirin should be taken if flushing.	Anti-neoplastic, immunomodulatory and immunosuppressive drugs.	CBC, AST, ALT, bilirubin levels, urine analysis.	Contraindicated during pregnancy and lactation
Fingolimod	0.5 mg, orally, daily	The first dose must be taken in a hospital facility due to cardiological risk.	Anti-neoplastic, immunomodulatory and immunosuppressive drugs.	CBC, AST, ALT Annual dermatological and ophthalmological evaluation	Contraindicated during pregnancy and lactation
Teriflunomide	14 mg, orally, daily.	Hair thinning	Anti-neoplastic, immunomodulatory and immunosuppressive drugs.	CBC, ALT, AST	Contraindicated during pregnancy and lactation
Interferon β	Interferon β 1a, 22 and 44 mcg, SC, 3 times a week	Association with depression.	No interactions	CBC, AST, ALT	No contraindications
	Interferon β 1a, 30 mcg, IM, weekly				
	Interferon β 1b, 300 mcg, SC, every other day				
	Pegylated Interferon β 1a, 125 mcg, SC, every 14 days				
Glatiramer acetate	20 mg, SC, daily or 40 mg, SC, 3 times a week.	Short-term infusion reaction (palpitation, flushing and chest tightness)	No interactions	CBC	No contraindications
PLEX	3-7 sessions, every other day	Hypocalcemia risk during sessions	No interactions	Blood pressure, calcium, coagulation tests.	No contraindications
Intravenous immunoglobulin (IVIg)	Initial dose: Up to 2 g/kg per cycle (most cases 0.4 g/kg per day for 5 days Infusion: starting at 0.01 mL/kg/min; in situation of clinical stability, increase it every 15-30 minutes up to 0.08 mL/kg/min *Mean of at least 1 hour per flask (5 g/flask) is recommended in the presentation widely available from SUS	IgA level dosage is recommended before start Attention to increased risk of thromboembolic events	No interactions	No need for routine examinations	Can be used safely during pregnancy and breastfeeding if the benefits surpass the risks.

Table 1. Cont.

Drug	Dose	Special issues	Interactions	Follow-up	Pregnancy and breastfeeding
Subcutaneous immunoglobulin	Dosage: Convert current monthly intravenous immunoglobulin dosage to weekly subcutaneous infusions of 1-2 mL/kg per week (total dosage is the same for the period: total in grams multiplied by 5 = volume in mL); infusion rate: 15-20 mL/hour/infusion site (high infusion rates during further treatment stages: up to 25-50 mL/hour/infusion site).	IgA level assay is recommended before start Attention to increased risk of thromboembolic events	No interactions	No need for routine examinations	Not assigned by FDA yet

ACEi: angiotensin-converting enzyme inhibitors; TPMT: thiopurine methyltransferase; CBC: complete blood count; AST: aspartate transaminase; ALT: alanine transaminase; Cr: serum creatinine; GFR: glomerular filtration rate; HBV: hepatitis B virus; HCV: hepatitis C virus; TST: tuberculin skin test; IGRA: interferon gamma release assay; NYHA: New York Heart Association; TB: tuberculosis; ULN: upper limit of normal; TSH: thyroid-stimulating hormone; T4: thyroxine; GBM: glomerular basement membrane; PML: progressive multifocal leukoencephalopathy; JCV: John Cunningham virus.

Table 2. Relative activity and length of action of the corticosteroids most used in Neurology.

	Dosage equivalency (mg)	Relative activity (hydrocortisone)	Relative mineralocorticoid activity	Duration of activity (h)	Neurological conditions
Prednisone	5	4	0.3	12-36	MG, NMOSD and others
Prednisolone	5	4	0.3	12-36	Sarcoidosis, NMOSD and others
Methylprednisolone	4	5	0	12-36	MS, NMOSD and others
Deflazacort	7.5	3	Minimal	24	Duchenne dystrophy
Dexamethasone	0.75	30	0	36-72	CNS tumor edema

Table 3. Monitoring routine for long-term corticosteroid use.

Side effects	Investigation	Periodicity
Systemic hypertension	Blood pressure	Every 6 months*
Diabetes	Blood glucose/ glycated hemoglobin	Before start*
Dyslipidemia and metabolic syndrome	Weight, height, BMI and lipids	Every 6 months*
Osteoporosis and fractures	BMD	Once a year * If stable, every two years
	Spine X-ray	Once a year
Glaucoma and cataracts	Ophthalmological consultation	Once a year

*Those must be tested also before initiation of long-term use.

for evaluation of signs and symptoms of adrenal insufficiency and steroid withdrawal.

AZATHIOPRINE

Azathioprine belongs to the group of thiopurines. It undergoes metabolization to 6-mercaptopurine (6-MP), a metabolite that has immunosuppressive effects and inhibits purine synthesis, reduces leukocyte proliferation and impairs immune response[12].

The main indications of azathioprine for neurological disease treatment are myasthenia gravis, NMOSD, primary central nervous system (CNS) vasculitis, immune-mediated myopathies, neuro-Behçet's disease (NBD) and chronic inflammatory demyelinating polyneuropathy (CIDP).

Hematological toxicity and the risk of myelosuppression are primary concerns associated with use of azathioprine, mostly related to low levels of thiopurine methyltransferase. Minor blood cell changes, including mild lymphopenia and increased mean corpuscular volume, may occur during treatment, but do not necessarily require drug discontinuation[13]. Other side effects include hepatotoxicity, nausea, vomiting and skin rash. Azathioprine has been associated with a low risk of malignancies[13].

METHOTREXATE

Methotrexate (MTX) is a folic acid antagonist that inhibits purine and pyrimidine synthesis, thus affecting DNA and RNA synthesis[14]. It disrupts inflammatory and neoplastic cell division, reduces the levels of some cytokines (thereby leading to reactive oxygen species (ROS) accumulation in T-cells) and inhibits inflammatory transcription factors[15].

MTX is widely used for managing several autoimmune disorders including sarcoidosis, immune-mediated myopathies and granulomatosis with polyangiitis (GPA). Patients on MTX may present incapacitating gastrointestinal side effects, mostly nausea and vomiting, and switching from oral to subcutaneous MTX may increase tolerance[16]. Other side effects include hepatotoxicity, stomatitis, pulmonary fibrosis, neurotoxicity (e.g., leukoencephalopathy), nodulosis, renal insufficiency and cytopenia[17]. Use of MTX has been associated with increased risk of lymphoproliferative disorders[18].

MYCOPHENOLATE MOFETIL

Mycophenolate mofetil (MMF) is a drug with immunosuppressive properties that acts in purine synthesis and has antiproliferative effects on T- and B-lymphocytes, with depletion of lymphocytic and monocytic cells and inhibition of interleukin production[19]. MMF is used in MG, NMOSD, autoimmune neuropathies and immune-mediated myopathies. It is also effective for treating systemic lupus erythematosus (SLE), vasculitis, rheumatoid arthritis and Takayasu arteritis[20].

The side effects of MMF are usually mild, mostly consisting of gastrointestinal complaints (e.g. diarrhea, vomiting and mild abdominal pain), and mild lymphocytopenia can also occur. MMF increases the risk of lymphoproliferative disorders, especially in patients infected by Epstein-Barr virus[21,22].

CYCLOSPORINE (OR CYCLOSPORINE A)

Cyclosporine reduces the cytosolic activity of calcineurin and proinflammatory cytokines (mainly IL-2) produced by T-lymphocytes. It is a corticosteroid-sparing drug used in management of inflammatory autoimmune neuromuscular disorders including generalized MG Class II-IV, dermatomyositis and idiopathic inflammatory myopathies and autoimmune neuropathies. It is usually reserved for refractory cases that have been treated with other agents (e.g. methotrexate, mycophenolate and azathioprine).

The common side effects of cyclosporine include arterial hypertension, hyperlipidemia, nephrotoxicity, hypomagnesemia, hyperkalemia and hypophosphatemia. Posterior reversible encephalopathy syndrome (PRES) induced by cyclosporine is rare.

CYCLOPHOSPHAMIDE

Cyclophosphamide is an alkylating agent that interferes in DNA synthesis and disrupts cell replication. Because of its effect, rapidly proliferating cells such as leukocytes are more susceptible to cyclophosphamide[23].

Cyclophosphamide is used for treatment of neurological conditions including autoimmune encephalitis, primary CNS vasculitis, immune-mediated myopathies, neuropsychiatric SLE and neurological manifestations of systemic vasculitis.

There are three major safety concerns relating to this drug: hematological toxicity, infertility and hemorrhagic cystitis[24]. Cyclophosphamide may cause neutropenia, leukopenia and bone marrow suppression at high doses, generally occurring within 7 to 14 days of administration[23]. Female infertility and premature menopause are associated with cumulative doses and advanced age[25]. Hemorrhagic cystitis may occur due to exposure of the bladder to acrolein, a metabolite of cyclophosphamide[26]. Increased water ingestion and normotonic saline administration before and during infusion can increase urinary dilution and reduce exposure to acrolein, thus preventing occurrence of acrolein-induced hemorrhagic cystitis. Mesna can be used as an alternative agent, as it metabolizes acrolein to a less toxic compound and protects against hemorrhagic cystitis. Other side effects include alopecia, mucositis, nausea, vomiting, hyponatremia, nephrotoxicity, cardiac toxicity and hepatotoxicity[24].

Cyclophosphamide increases the risk of neoplasia, especially bladder cancer, and lymphoproliferative disorders[27].

ANTI-TUMOR NECROSIS FACTOR-

Tumor necrosis factor- (TNF) is essential for macrophage and phagosome activation, differentiation of monocytes into macrophages, neutrophil and macrophage recruitment and granuloma formation and maintenance[28]. TNF inhibitors (anti-TNF) are used to manage inflammatory conditions (e.g. rheumatoid arthritis, sarcoidosis and Behçet's disease).

Injection site reactions (ISR) are common side effects associated with anti-TNF therapies. They typically occur within the first month of treatment and last 3-5 days. Infusion reactions to infliximab are classified as acute (those that occur within 24 hours in 90% of infusions) or delayed (those that develop within 1-14 days of infusion), and they can be IgE-mediated (anaphylactic) including hypotension, bronchospasm, wheezing and urticaria or anaphylactoid (nonallergic)[29,30]. Neutropenia and infectious complications, including bacterial infections (particularly pneumonia), herpes zoster infection, tuberculosis and opportunistic infections, are adverse effects of this drug. Reactivation of hepatitis B virus can occur in chronic carriers. Although a causal relationship remains uncertain, this drug class should not be given to patients with demyelination[31]. Other adverse effects include heart failure, sarcoid-like pulmonary disease or fibrotic/interstitial pulmonary disease, hepatic involvement (acute liver failure, hepatitis and cholestasis) and cutaneous involvement (psoriasiform eczema, eczema, xerosis cutis, palmoplantar pustulosis and psoriasis)[32–34]. Rare cases of autoimmune disorders, such as lupus-like syndrome and positive antinuclear antibody titers in patients who were negative at baseline, have been reported.

ANTI-CD20

Rituximab, ocrelizumab and ofatumumab are monoclonal antibodies that selectively target CD20, a cell surface antigen expressed in a broad range of B-cells. These drugs preferentially bind to CD20 on the cell surface of B-cells, which consequently leads to cell death through numerous mechanisms, including complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis[35].

Anti-CD20 therapies are used for managing several neurological disorders, including MS, NMOSD, MG, immune-mediated myopathies, autoimmune encephalitis, CNS vasculitis and sarcoidosis. They are associated with high infection rates, especially of herpes virus infection, but most cases are mild. Patients on long-term anti-CD20 therapy are at risk of hypogammaglobulinemia with resultant higher risk of recurrent infections. They should be followed up with regular cancer screening examinations, and any suspicious lesions must be further assessed to rule out malignancies[36].

ALEMTUZUMAB

Alemtuzumab is a humanized monoclonal antibody that is specific to CD52, a lymphocytic cell surface glycoprotein of unknown function. This drug causes profound depletion of peripheral lymphocytes and leads to long-lasting changes in adaptive immune response, and mild reduction of innate immune system cells (neutrophils and NK cells)[37]. It has been approved for treating patients with highly active MS.

Severe autoimmune-related adverse events have been reported from use of alemtuzumab. The most relevant adverse effects are thyroid diseases (17% after three years of exposure), immune thrombocytopenia (ITP) (2.3%) and nephropathies (0.2%)[38]. Before treatment, baseline assessments should be performed, including thyroid hormone levels, platelet count, serum creatinine and urine analysis. A specialist should be consulted for advice on managing immune-related adverse events[39].

Infections (commonly herpes simplex or zoster infection) may also occur. Prophylaxis is necessary until normal lymphocyte counts have been restored[40].

NATALIZUMAB

Natalizumab is a humanized antibody that binds to a specific cell adhesion molecule called integrin. Integrins are expressed on the cell surface of all leukocytes, except neutrophils. This drug binds to integrin a4ß1 and a4ß7 subunits and blocks leukocytes from crossing the blood-brain barrier[41].

Natalizumab is approved for treatment of patients with highly active relapsing-remitting MS (RRMS). Anti-JC virus (JCV) antibody serological status is used to determine treatment duration. Treatment can be discontinued after 24 infusions; however, new data has recently shown that treatment can be extended over 24 months with dosing intervals of 6 weeks[42].

Progressive multifocal leukoencephalopathy (PML) is a major adverse event associated with continuous natalizumab therapy. The risk factors for PML include the number of infusions, anti-JCV status and index and prior use of immunosuppressants[43].

Patients should be tested for anti-JCV antibody status before treatment is started and should be retested during treatment every 6 months to detect seroconversion or index augmentation[41]. Nevertheless, regular 24-month treatment with natalizumab in patients testing positive for anti-JCV antibodies appears to be safe[43].

CLADRIBINE

Cladribine is an agent that causes profound lymphopenia due to cytotoxicity, particularly in lymphocytes. It disrupts cellular metabolism, inhibits DNA synthesis and repair and induces lymphocyte apoptosis[44]. Recently, an oral formulation of cladribine has been approved for treatment of highly active relapsing MS in Europe, USA and Brazil[45].

Cladribine has a good overall safety profile but, as expected, severe lymphopenia can occur[46]. However, lymphocyte counts tend to recover after discontinuation of treatment. The malignancy rate in cladribine-treated patients is almost the same as the rate in the overall population[46].

SPHINGOSINE 1-PHOSPHATE RECEPTOR MODULATORS

Fingolimod and siponimod are sphingosine-1-phosphate (S1P) receptor modulators that acts as functional receptor antagonists. They inhibit the S1P1 receptor and block lymphocyte migration from lymph nodes to peripheral blood and through endothelial barriers such as the blood-brain barrier[47]. Fingolimod is used for treatment of RRMS.

S1P receptors are present in different organs. It is thus recommended that cardiac and ophthalmological evaluations should be performed before treatment is started, in order to rule out preexisting conditions that may increase the risk of cardiovascular events and macular edema through continuous use of fingolimod[47].

Patients should be given the first dose of fingolimod in a hospital setting and should be monitored for severe bradycardia and atrioventricular block over a six-hour period. Monitoring of lymphocyte counts should be performed, as fingolimod can cause lymphopenia and sometimes severe lymphopenia (≤ 200/μL). Fingolimod-treated patients are at higher risk of herpes zoster infection and also other opportunistic infections such as TB and cryptococcosis[48]. Gradual withdrawal of fingolimod over a four-week period, in order to prevent rapid lymphocyte release and severe disease activation, has been suggested[49].

DIMETHYL FUMARATE

Dimethyl fumarate (DMF) has been approved for treatment of RRMS. It has immunomodulatory and neuroprotective effects and acts by shifting the balance between pro-inflammatory and anti-inflammatory immune responses and altering the composition of lymphocyte subpopulations, thus resulting in induction of T-cell apoptosis, inhibition of activation of antigen-presenting cells and downregulation of vascular cell adhesion molecule expression in brain endothelium and of transmigration across the blood-brain barrier[50].

Real-life data and data from pivotal studies have shown that adverse events are usually mild to moderate, including flushing, diarrhea and nausea, and seldom require drug discontinuation. Flushing can be managed with prophylactic use of aspirin and gastrointestinal events can be improved through food and initial-dose titration[51].

DMF can cause severe and persistent lymphopenia, proteinuria and hematuria. Despite its safety, common infections such as nasopharyngitis and upper respiratory tract infections have been reported. PML has been described in a few older patients with prolonged lymphopenia (0.5×10^9/L)[52].

TERIFLUNOMIDE

Teriflunomide is an active metabolite of leflunomide with immunosuppressive activity that selectively inhibits dihydroorotate dehydrogenase (DHODH), a mitochondrial enzyme that is essential for the *de novo* pyrimidine nucleotide synthesis pathway and is expressed at high levels in proliferating lymphocytes. This drug reduces T-cell and B-cell activation and decreases their ability to cross the blood-brain barrier[53].

Teriflunomide has been approved for treatment of RRMS and clinically isolated syndrome (CIS). It is a sustainable, safe drug. Common adverse events include hair thinning, nausea, diarrhea and alanine aminotransferase alterations[54].

This drug is contraindicated for use in pregnant women and child-bearing women who are not using reliable contraception methods, since it can cause embryo-fetal developmental toxicity and malformations[54]. If pregnancy occurs during treatment, the patient must undergo an accelerated drug elimination procedure, with administration of cholestyramine or charcoal powder[55].

INTERFERON BETA

Interferon beta (IFNβ) acts on the immune system through a variety of mechanisms including inhibition of pro-inflammatory cytokines, inhibition of T-cell activation, stimulation of anti-inflammatory cytokine production and restriction of leukocyte migration across the blood-brain barrier[56].

IFNβ-derived drugs are indicated for RRMS. The treatment has proven safety. Common adverse events include flu-like symptoms, which can be managed with dose titration and symptomatic medication administered before injection. Lymphopenia and increased aminotransferase (AST and ALT) levels may occur and may eventually lead to drug withdrawal[57]. A previous history of depression is a known risk factor for developing new depressive episodes within the first six months of treatment and it is a contraindication for use of IFNβ[58]. IFNβ has been proved safe during pregnancy and lactation[59].

GLATIRAMER ACETATE

Glatiramer acetate (GA) comprises four amino acids (L-glutamic acid, L-lysine, L-alanine and L-tyrosine) that form a synthetic analog of myelin basic protein (MBP). Its precise mechanism of action is not fully understood but involves immunomodulatory effects (Th1-Th2 shift and increased regulatory T-cells) and neuroprotective effects[60].

GA is indicated for treating RRMS. Common adverse events associated with GA include mild injection site reactions (e.g. pain, erythema, edema and nodules) and mild immediate post-injection reactions (e.g. vasodilatation, chest pain, tachycardia and palpitation)[61]. Patients on GA treatment are not at increased risk of malignancies or infections and do not require monitoring[62]. It is a safe therapy during pregnancy and lactation[63].

INTRAVENOUS IMMUNOGLOBULIN

Intravenous immunoglobulin (IVIg) is a pool of functionally and structurally distinct human immunoglobulin G (IgG) from different individuals. It acts through various immune mechanisms to reduce autoreactive antibodies and causes indirect reduction of TNF-α and IL-10 and decreased macrophage activation[64].

IVIg is indicated for treatment of acute inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome) and its variants, except typical Miller-Fisher syndrome; multifocal motor neuropathy (MMN) with conduction block; small-fiber neuropathy with autoimmune dysautonomia; chronic inflammatory demyelinating polyneuropathy (CIDP); myasthenia gravis; relapsing myelin oligodendrocyte glycoprotein antibody-associated disease in both children and adults; immune-mediated myopathies (dermatomyositis, immune-mediated necrotizing myopathy and overlapping syndromes) and dysphagia in sporadic inclusion body myopathy; idiopathic and paraneoplastic autoimmune encephalitis; and stiff-person syndrome and its variants.

Mild to moderate adverse reactions to IVIg therapy can occur. Patients who suffer from serum IgA deficiency are at higher risk, especially during the first administration of IVIg. These reactions include skin rash, headache, fever, thrombophlebitis, thromboembolic events, anaphylactic reactions, anaphylactoid reactions, aseptic meningitis, vestibular symptoms, myalgia, cramps, diarrhea, hypertensive crisis, hypotension, cardiac arrhythmias, chest pain, hemolytic anemia, transient neutropenia, acute renal failure, pseudohyponatremia and transfusion-related acute lung injury (TRALI). A slow infusion rate and pre-hydration with 500 mL of 0.9% saline solution for adults can minimize these reactions[65].

SUBCUTANEOUS IMMUNOGLOBULIN

Subcutaneous immunoglobulin (SCIg) and IVIg have similar mechanisms of action and clinical indications. SCIg is indicated for treatment of patients with serious adverse effects from IVIg or when venous access is unavailable; and in situations of CIDP, MMN, immune-mediated myopathies and autoimmune MG (during acute exacerbations).

SCIg is well tolerated in general and safer than IVIg, but it can cause local granuloma-like reactions, fever, skin rash, cellulitis, anaphylaxis due to inadvertent vascular injection, skin eruptions, pruritus and joint pain[65,66].

THERAPEUTIC PLASMA EXCHANGE

Therapeutic plasma exchange (TPE or PLEX) is a therapeutic procedure using an apheresis device in which the plasma is separated from whole blood, removed and replaced with a substitution fluid (albumin or saline). PLEX requires adequate venous access (a central venous catheter). It usually involves 3-7 sessions with time intervals of 24-48 h between sessions, and typically 1-1.5 plasma volumes are removed per procedure[67].

PLEX is a well-established treatment for MG, Guillain-Barré syndrome, CIDP, paraproteinemic demyelinating polyneuropathies, chronic focal encephalitis (Rasmussen encephalitis), Lambert-Eaton myasthenic syndrome, MS (acute exacerbation) and NMOSD (during acute exacerbations).

Occurrences of adverse events in PLEX are associated with several factors including preexisting conditions. Severe symptoms are mostly associated with addition of infusion fluid or anticoagulants (citrate) during the procedure. Citrate can cause symptomatic hypocalcemia, and patients may develop allergic reactions due to the infusion fluid[68]. Hypotension, arrhythmias and tetany may occur; therefore, patient monitoring is required during the procedure[69].

RECOMMENDATIONS FOR VACCINATION AND PROPHYLAXIS FOR PATIENTS UNDERGOING TREATMENT WITH IMMUNOSUPPRESSIVE DRUGS

Regular evaluation of immunization schedules is an essential part of consultations for immunosuppressed patients. Safety and immunogenicity are the major concerns regarding vaccination. The immunization schedule should be updated four weeks before immunosuppression is started[70]. When the therapy cannot be delayed, the minimum interval from vaccine dose to treatment start is two weeks[71–73].

Live-agent vaccines (e.g. yellow fever, oral polio and measles-mumps-rubella) have higher risk of severe adverse effects in patients under immunosuppression. Patients under mild to moderate immunosuppression can be considered for live-agent vaccine if their clinical and epidemiological profile is favorable[71]. Patients with a controlled autoimmune disease who are at higher risk of becoming infected (e.g. through living in yellow fever endemic areas) might be considered to be candidates to receive the vaccine. Contacts of immunosuppressed patients should not receive oral polio vaccine due to the risk of viable virus transmission. Maternal exposure to biological agents during pregnancy is a contraindication for application of rotavirus vaccine and BCG vaccination until the child is six months of age[71]. Table 4 summarizes a routine for immunization of patients before, during and after immunosuppression.

OPPORTUNISTIC INFECTIONS, SCREENING AND PROPHYLAXIS FOR PATIENTS UNDERGOING TREATMENT WITH IMMUNOSUPPRESSIVE DRUGS

Patients on immunosuppressive therapy are highly susceptible to opportunistic infections. Identification of risk factors, clinical and laboratory monitoring, vaccination and patient education are key to preventing opportunistic infections in these patients.

Corticosteroids have been associated with invasive fungal infections, especially *Candida* sp. and *Pneumocystis jirovecii*

Table 4. Vaccination issues before, during and after immunosuppression.

Vaccination pre-immunosuppression:	Vaccination on immunosuppression:	After immunosuppression:
Non-live vaccines should be administered at least two weeks prior to treatment; Live vaccines should be given at least one month prior to treatment; Pneumococcal vaccine should be given to all immunosuppressed patients; Influenza vaccine should be given yearly for patient and household.	Generally, no live vaccines should be given; All patients should receive HPV vaccine if age-appropriate and a yearly influenza vaccine (inactivated); Meningococcal vaccines should be repeated every five years if immunosuppression is ongoing.	After 4 months off therapy, check baseline serology (VZV, measles, mumps, rubella, hepatitis A and B, diphtheria, tetanus and *H. influenzae b*), if antibodies are present, polio/pertussis vaccines do not need to be re-administered; If lymphocyte count > 1,000, initiate re-immunization schedule; IVIg interferes with antibody response to live vaccines. These should be delayed until 9 months (if 1 g/kg/dose given) or 11 months (if 2 g/kg/dose given).

HPV: human papillomavirus; VZV: varicella-zoster virus.

(PJP). Administration of sulfamethoxazole-trimethoprim 2-3 times a week (or dapsone when a patient is allergic) is known to prevent PJP infection in patients with ANCA-positive vasculitis (especially granulomatosis with polyangiitis during induction treatment) and those receiving corticosteroids with other agents such as azathioprine, cyclophosphamide and methotrexate[74].

Use of thiopurines, MTX and infliximab has been associated with increased risk of *C. difficile*-associated disease[75]. Vaccination is able to prevent pneumonia and meningitis caused by *Streptococcus pneumoniae* (revaccination is recommended because antibody levels decrease over time)[76].

All patients should be evaluated to determine the risk of latent or active TB (especially those on corticosteroids, cladribine, teriflunomide and anti-TNF) through tuberculin skin testing or interferon-gamma-release assays (IGRAs). A definitive diagnosis of latent TB is established through identifying risk factors and through positive screening tests, even without clinical or radiographic evidence of active TB. The European Crohn's and Colitis Organization (ECCO) guidelines recommend delaying anti-TNF therapy for TB patients for at least three weeks after starting chemoprophylaxis with isoniazid or rifampicin[77].

Patients should be screened for hepatitis B virus (HBV) (HBsAg, anti-HBc and anti-HBs) before immunosuppression because of the risk of reactivation of HBV replication[78]. It is also recommended to test for HIV infection. Corticosteroids increase the CD4 population and decrease the HIV viral load, while AZA therapy is associated with increased viral replication[79]. Varicella-zoster virus can cause encephalitis, pneumonia, hepatitis and death, particularly among older patients and those using anti-TNF, fingolimod and corticosteroids. Thus, active vaccination is recommended[80]. Over 90% of the world's population is infected with Epstein-Barr virus (EBV), and seropositivity increases with age[81]. AZA has been associated with EBV hepatitis, mucocutaneous ulcers and hemophagocytic syndrome, and IFX has been linked to severe complications or atypical presentations[82]. All patients should be vaccinated against human papillomavirus (HPV), and women require more frequent gynecological examinations and cervical screening[83].

In conclusion, the follow-up for patients with autoimmune diseases is a complex task, and correct management of immunosuppressive or immunomodulatory drugs is crucial for ensuring better outcomes. Knowledge of doses, adverse effects and follow-up details for each drug used is essential for attaining a balance between the risks and benefits of immunosuppression. Vaccination, prophylaxis for infections and adverse effect screening are important issues to be considered before, during and after the treatment. This review may serve as a guide for general neurologists, to help in management of patients under treatment with immunosuppressive or immunomodulatory drugs.

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