

First-line immunosuppression in neuromuscular diseases

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ABSTRACT

Autoimmune neuromuscular diseases are common and often treatable causes for peripheral nervous system dysfunction. If not optimally managed, they result in meaningful impairments and disability. The treating neurologist should aim to maximise clinical recovery with minimal iatrogenic risk. This requires careful patient and medication selection, appropriate counselling and close monitoring of clinical efficacy and safety. Here, we summarise our consensus departmental approach to first-line immunosuppression in neuromuscular diseases. We combine multispecialty evidence and expertise with a focus on autoimmune neuromuscular diseases to create guidance on starting, dosing and monitoring for toxic effects of the commonly used drugs. These include corticosteroids, steroid-sparing agents and cyclophosphamide. We also provide efficacy monitoring advice, as clinical response informs dosage and drug choice. The principles of this approach could be applied across much of the spectrum of immune-mediated neurological disorders where there is significant therapeutic crossover.

INTRODUCTION

Autoimmune myopathies, neuropathies and myasthenic syndromes have differing pathogenesis and diverse clinical presentations.^{1–3} Immunosuppressive treatment (generalised suppression of the immune system) and immunomodulatory treatment (supplementation or alteration of the immune response without suppression) are based on the sole or combined use of corticosteroids, intravenous immunoglobulin, plasma exchange, cyclophosphamide or rituximab in the acute phase. Oral immunosuppressant steroid-sparing agents are used completely alone, or more commonly in combination with—and then after—corticosteroids, enabling corticosteroid reduction and remission maintenance. There are completed randomised controlled trials of immunosuppression

in Guillain-Barré syndrome,⁴ chronic inflammatory demyelinating polyneuropathy,⁵ myasthenia gravis,⁶ inflammatory myopathies³ and others. However, there is no consensus on an approach to immunomodulatory treatment. The choice of a therapy in individual cases should be based on the likely treatment efficacy in relation to the disease mechanisms, individual clinical features of the patient and their disease, and the risk of complications.

The current advice on prescribing and monitoring of these drugs is derived and modified from rheumatology, dermatology, oncology and haematology guidelines. However, there are patient and disease characteristics specific to neuromuscular disorders with respect to toxicity and efficacy monitoring that require some tailoring. Previous publications in this journal have discussed rituximab, azathioprine and the use of plasma exchange in neurological disorders in detail.^{7–9} Here, we describe an approach to safe, sensible and responsive use of first-line immunosuppression agents in neuromuscular diseases based on best available evidence, multispecialty input and consensus expert neuromuscular clinical opinion. Online supplemental documents 1–7 linked to this article can be used to support informed consent of patients and guide pretreatment screening and safety monitoring thresholds for action. We recommend a range of disease-specific validated clinical outcome measurement tools, most of which are freely available online.

This approach aims to optimise clinical outcomes and minimise complications as any degree of immunosuppression, although with medications in common use, represents a relatively high-risk intervention for the practising clinical neurologist.

Mechanism of action

Knowledge of drug-specific mechanisms of action informs appropriate selection, use and expectations of response, as well

Drug	Mechanism of action	Immune consequences
Corticosteroid	Inhibits gene transcription for secretion of inflammatory cytokines	Reduces leucocyte migration, phagocytic function of neutrophils and monocytes, and T-cell function
Azathioprine	Purine antimetabolite: inhibits resting (G1) and DNA synthesis (S) phases of the cell cycle	Apoptosis of T lymphocytes
Methotrexate	Folic acid antagonist; inhibits purine synthesis	Specific immune cell targets unknown
Mycophenolate mofetil	Blocks de novo purine synthesis	Antilymphocyte (T-cell and B-cell) action. Less toxic than azathioprine
Cyclophosphamide	DNA alkylation: blocks all phases of cell cycle	Anti T-cell and B-cell activity
Rituximab	Monoclonal anti-CD20 antibody	Reduces pathogenic antibody production by reducing CD20 positive B cells and the number of new plasma cells (CD20 negative but develop from B-lineage). Reduces pathogenic antibodies and disrupts other B-cell roles (such as antigen-presenting cells) in the immune system

as understanding of adverse effects, timely monitoring and when to action a change in treatment (table 1).

safety and efficacy, and regularly reviewing to consider if ongoing treatment is still required (figure 1).

APPROACH TO IMMUNOSUPPRESSION IN NEUROMUSCULAR DISEASES

We use a clinical, patient-centred approach to select and use of immunosuppressant medications. Within broad boundaries, the dose and duration of treatment largely depends on clinical response, and it is essential to set stopping criteria before starting. We recommend a systematic approach to patient assessment for each medication because of the potential for adverse events, to protect both the patient from harm and the prescriber from potential litigation. The main elements of the approach include establishing eligibility, practising fully informed consent procedures, inducing treatment appropriately, maintaining monitoring for

Eligibility

The diagnosis of an autoimmune neuromuscular disease should be made as thoroughly as possible, with appropriate and ample laboratory support, before considering treatment. This includes a tissue diagnosis where possible and relevant, especially in vasculitis or where the first-line response was not as expected. After starting treatment, it is virtually impossible to collect diagnostically relevant pathological data retrospectively. The diagnosis and supporting investigations should be clearly documented, preferably alongside diagnostic criteria where available. Previous *Practical Neurology* publications have discussed the diagnostic approaches to the conditions mentioned here.¹⁰⁻¹⁴

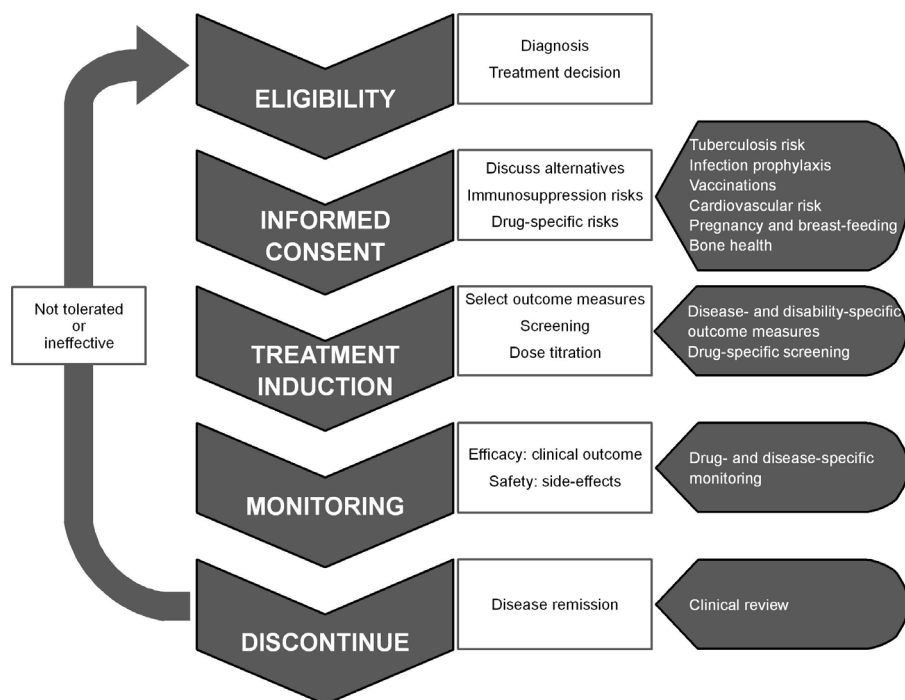


Figure 1 Approach to immunosuppression in neuromuscular diseases.

Table 2 Immunotherapy choices in inflammatory neuromuscular diseases

	Steroids	Intravenous Ig/SCIg	AZA	MTX	MMF	CYC	PLEX
GBS	No	1	No	No	No	No	1
CIDP	1	1	2	No	3	3	3
MMN	No	1	No	No	No	2	No
Vasculitic neuropathy	1	No	2	3	*	1	No
Polymyositis	1	2	2	2	3	*	*
Dermatomyositis	1	2	2	2	3	*	*
Myasthenia gravis	1	cr>m	2 (m)	3 (m)	2 (m)	*	1

1 indicates first-line response, 2 indicates second-line response and 3 indicates third-line response.
 *May consider in individual cases.
 AZA, azathioprine; CIDP, chronic inflammatory demyelinating polyneuropathy; cr, treatment of myasthenic crisis; CYC, cyclophosphamide; GBS, Guillain-Barré syndrome; m, maintenance treatment; MMF, mycophenolate mofetil; MMN, multifocal motor neuropathy; MTX, methotrexate; No, not recommended; PLEX, plasma exchange; SClg, subcutaneous immunoglobulin.

The treatment choice depends on the disease; table 2 provides a simplified summary of preferred drug choice, developed by neuromuscular consultants in our department. It is essential to consider carefully patient comorbidities and disease severity.

Informed consent

Before 2020, UK General Medical Council ethical guidance regarding informed consent was based on the Bolan criteria,¹⁵ the main principles of which stated that one should inform patients of all potential minor adverse events if they occur frequently (1/10–1/100) and of any serious adverse event, even if likelihood is very small (<1/10 000) with the test being that a reasonable body of clinicians would do the same. The WHO defined a serious adverse event as any outcome potentially resulting in death, permanent or long-term physical disability or disfigurement, medium or long-term pain, or admission to hospital; or other outcomes

with a long-term or permanent effect on a patient's employment, social or personal life.¹⁶

Based on these criteria, we prepared a set of patient information booklets for each of the medications discussed in this paper, which should provide adequate, generalised information on potential risk (online supplemental file 8). Each booklet outlines, in clear and simple language, basic information about the drug, why it is used, how it is taken, what are the possible adverse effects and their approximate frequency. We also highlight the safety measures in place to minimise risk, including monitoring and prophylaxis in certain situations. We discuss alternative options and expected outcome or prognosis if the patient chooses not to take this particular medication. We give some basic references with advice on where to find further patient-appropriate information.

However, the Montgomery judgement of March 2015 requires doctors to provide information about all 'material risks', as well as any to which it would be reasonable for them to think the individual would attach significance.¹⁵ This allows for a more personalised discussion depending on the individual. This goes far beyond the scope of a generic patient information booklet, and must be informed by the patient-physician relationship on an individualised basis.

Magnitude of individual risk

As far as possible, clinicians should consider risk factors for any individual in the context of the presenting disease, its severity and threat, and the potential risks of the considered treatment.

Pretreatment recognition of renal, liver and respiratory disease allows for appropriate drug selection and risk minimisation in chronic renal impairment (table 4) and identification of those at high risk at risk for tuberculosis (TB) (figure 2) or *Pneumocystis jirovecii* reactivation (figure 3). Cardiovascular risks should be assessed and addressed with routine primary prevention before starting treatment in accordance to Q-RISK V.2 or other population-specific, validated risk calculator.¹⁷ It is also important to consider current

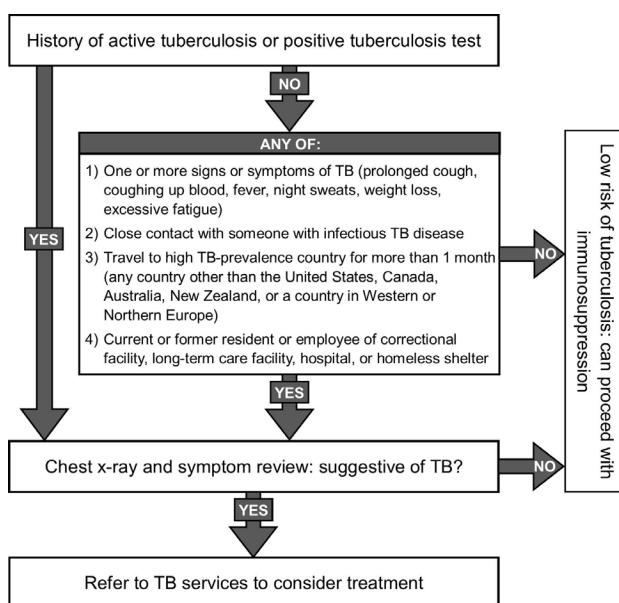


Figure 2 Algorithm for the consideration of tuberculosis (TB) treatment.

Table 3 Actionable events in preimmunosuppression comorbidity screening

Situation	Recommendation
Suspicion of parenchymal lung disease	Smoking cessation advice Lung function tests X-ray of the chest±high-resolution CT scan of the chest Consider referral to a respiratory physician
HIV, HBV and HCV	Consider antiviral treatment prior to immunosuppression (discuss with specialist)
Abnormal liver biochemistry (AST or ALT>100 IU/L)	Not an absolute contraindication Select less hepatotoxic drug: MMF instead of AZA
Abnormal synthetic liver function	Not an absolute contraindication Increased risk of toxicity, except MMF
Chronic renal impairment (CRI)	Investigate cause for newly identified CRI Alter dose/frequency and monitoring (table 14)
Cardiovascular risk	Primary prevention pretreatment
Previous malignancy	Not an absolute contraindication Routine population screening recommended

ALT, alanine transaminase; AST, aspartate aminotransferase; AZA, azathioprine; HBV, hepatitis B virus; HCV, hepatitis C virus; MMF, mycophenolate mofetil; MTX, methotrexate.

and future fertility and conception, breast feeding (table 6) and other physiological states, such as bone health (figure 4). The rheumatology literature strongly recommends the following as minimum pretreatment screening,¹⁸ with actionable events outlined in table 3:

- ▶ Height, weight, blood pressure and vascular risk assessment.

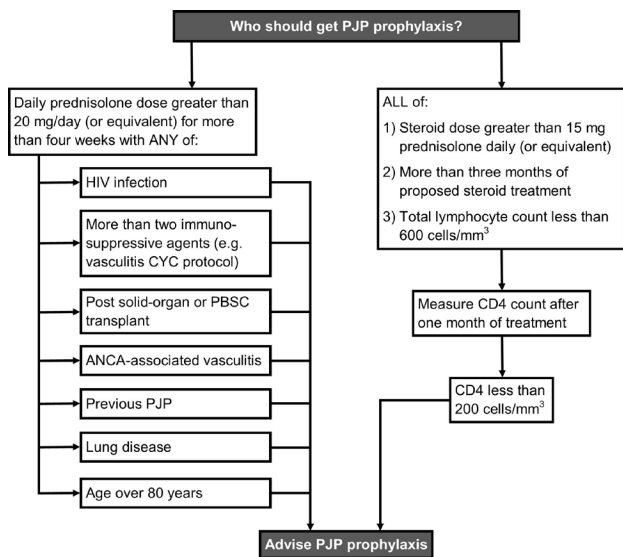


Figure 3 Algorithm for the consideration of *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis; ANCA, antineutrophil cytoplasmic antibody; CYC, cyclophosphamide; PBSC, peripheral blood stem cell.

- ▶ Full blood count, creatinine/calculated glomerular filtration rate, alanine aminotransaminase and/or aspartate aminotransferase, albumin, vitamin D and calcium.
- ▶ History and examination for respiratory disease.

TB risk

The risk of reactivation of latent TB should be considered in those receiving prednisolone at doses higher than 15 mg/day (or equivalent) for more than 6 weeks, those taking tumour necrosis factor- α (TNF- α) inhibitors and those taking antivascular treatment (combination therapy with pulsed cyclophosphamide and high dose corticosteroids).¹⁹ Figure 2 shows an algorithm for assessing TB risk. TB treatment should always be given under the care of an experienced respiratory physician.

***P. jirovecii* pneumonia prophylaxis**

P. jirovecii (previously known as *P. carinii*) is an obligate extracellular fungus that infects most children during childhood and is latent in up to 70% of non-HIV-infected adults. Reactivation causing *P. jirovecii* pneumonia has a mortality rate of 17%, rising to over 50% in the critically ill.²⁰ Data to support *P. jirovecii* prophylaxis in all patients taking high-dose corticosteroids (20 mg or more of prednisolone for 4 or more weeks) are weak and based on a historical, retrospective case series of 116 non-HIV-infected patients over a 7-year period in one institution with multiple and variable comorbidities alongside corticosteroid treatment.²¹ The potential adverse event rate of prophylactic treatment itself must be considered in comparison.

In rheumatoid arthritis, the risk of *P. jirovecii* pneumonia is 1.9%,²² and routine prophylaxis is not advised in any current UK rheumatology guidelines. In acute leukaemia, solid organ transplant and stem-cell transplantation *P. jirovecii* pneumonia occurs in 6.2% of patients without prophylaxis and there is an 85% reduction in infection rates with prophylaxis; this is the basis for *P. jirovecii* prophylaxis in national haemato-oncology guidelines.^{23 24} Other specific risk factors beyond corticosteroid use that increase risk of *P. jirovecii* pneumonia include a CD4 count below 200 cells/mm³, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, older age, lung disorders and TNF- α inhibition; cumulative immunosuppressants also confer higher risks.²⁵⁻²⁷ In lower-risk autoimmune conditions (such as the neuromuscular conditions in context here), it is sensible to consider *P. jirovecii* prophylaxis only when prolonged corticosteroid treatment coincides with another significant risk factor for *P. jirovecii* pneumonia.²⁸

We recommend prophylaxis with cotrimoxazole 960 mg three times a week for anyone taking more than 20 mg prednisolone for more than 4 weeks in combination with any of: concomitant HIV infection; age above 80 years; underlying lung disease; previous

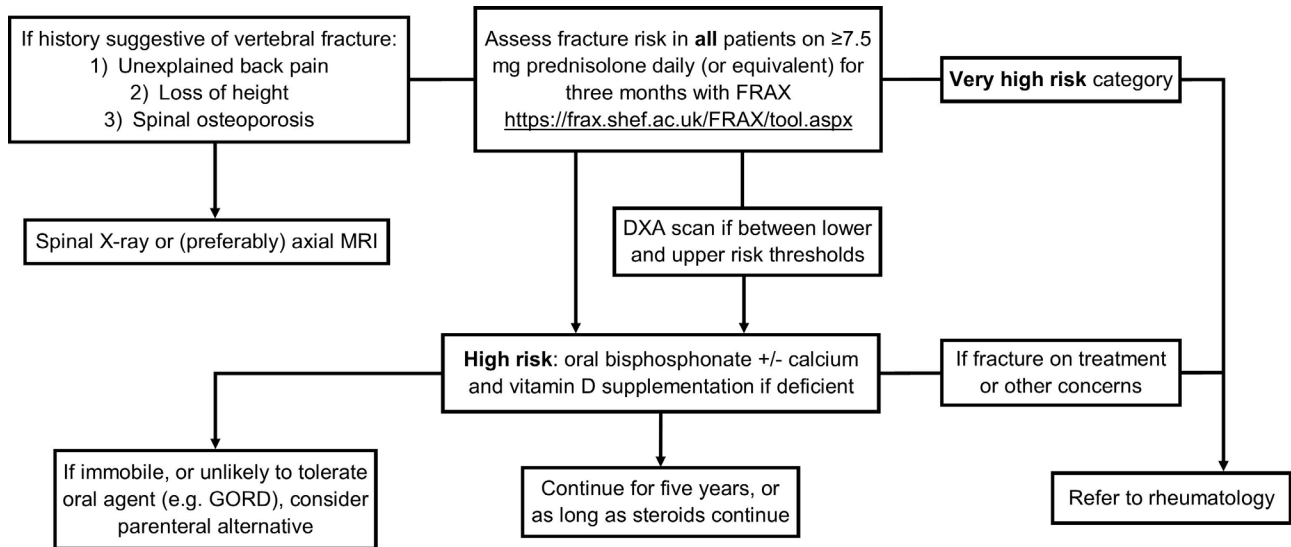


Figure 4 Assessment and treatment of bone health. DXA, dual-energy X-ray absorptiometry; GORD, gastro-oesophageal reflux disease.

P. jirovecii pneumonia; history of ANCA-associated vasculitis; previous solid organ or peripheral blood stem-cell transplant; or more than two other immunosuppressant medications (this includes vasculitis treatment, where corticosteroids and cyclophosphamide are followed by a steroid-sparing agent). In addition, if a patient has a total lymphocyte count below 600 cells/mm³ at baseline, and is planned to have a course of prednisolone of greater than 15 mg daily for at least 3 months, their CD4 count should be measured 1 month into treatment and prophylaxis recommended if the CD4 count is below 200 cells/mm³.^{21 26 28} Figure 3 summarises this advice.

Prophylaxis should be continued for as long as steroids are taken. Reactivation of infection must be balanced against the adverse effect profile of prophylaxis; for cotrimoxazole, this includes non-fatal adverse reactions such as rash, gastrointestinal

symptoms, *Clostridioides difficile* colitis, Stevens-Johnson syndrome and toxic epidermal necrolysis. Fatal anaphylactic reactions can occur at a rate of 15–25 reactions per million treated. This does not include drug interactions: methotrexate and cotrimoxazole in combination increase the risk of bone-marrow failure. Inappropriate antibiotic use adds to the burden of antimicrobial resistance in *P. jirovecii* pneumonia.²⁹

The alternatives to cotrimoxazole, such as dapsone, atovaquone and nebulised pentamidine, are significantly less effective and, in the case of pentamidine, not straightforward to deliver. They should only be considered when absolutely necessary.

Bone health

Bone health requires careful consideration in neuromuscular patients for two reasons. First, the typical corticosteroid dose used in neuromuscular disease

Table 4 Immunosuppression safety in pregnancy and breast feeding

	Periconception	T1	T2/T3	Breast feeding	Paternal exposure
Prednisolone ³⁶	Yes	Yes	Yes	Yes	Yes
Intravenous MP ³⁶	Yes	Yes	Yes	Yes	Yes
AZA ³⁸	Yes	Yes	Yes	Yes	Yes
MTX ≤ 25 mg/week ^{38 39}	Stop 1 month in advance	No	No	No	Yes
MMF ³⁸	Stop 6 weeks in advance	No	No	No	See text
CYC ³⁸	No	No*	No*	No	No
Intravenous Ig ^{37 38}	Yes	Yes	Yes	Yes	Yes†
Rituximab ^{7 38}	Consider stopping at conception‡	Severe disease if no alternatives‡	Severe disease if no alternatives§	Yes†	Yes†

*Only consider in severe life or organ-threatening maternal disease.

†Limited data available.

‡Can consider in severe maternal disease if no pregnancy-compatible alternatives available.

§If used in third trimester, avoid live vaccinations in infant until 6 months of age.

AZA, azathioprine; CYC, cyclophosphamide; Ig, immunoglobulin; MMF, mycophenolate mofetil; MP, methylprednisolone; MTX, methotrexate.

Table 5 Disease-specific outcome measures in autoimmune neuromuscular diseases

Condition	Established disability measure	MCID
Chronic inflammatory demyelinating polyneuropathy	MRC sum score* ⁵⁸	±2 points
	CIDP-RODS† ^{59 60}	±4 points (logit scale)
	Vigorimeter (kPa)‡ ⁶¹	±8 kPa
	10 m timed walk (s) ⁶² ONLS ^{60 63}	±28% change
Other neuropathy /neuromyotonia	INCAT† ⁶⁴	±1 point
	Berg balance scale† ⁶²	±8 points
	ABC balance score† ⁶⁵	<50%: low function
	Tremor scale† ⁶⁶ Myotonia behaviour scale† ⁶⁷	
Multifocal motor neuropathy	MRC sum score* ⁵⁸	±2 points
	Vigorimeter (kPa)‡ ⁶¹	±8 kPa
	MMN-RODS† ⁶⁸	±4 points (logit scale)
	ONLS ^{60 63}	
Inflammatory myopathy	MRC sum score* ⁵⁸	±2 points
	Timed up and go 3 m walk (s) ⁶⁹	
	CK	±30% change
	HAQ Score† ⁵⁷	±15% change
	Physician global activity assessment ⁷⁰	±20% change
	Patient/parent global activity assessment ⁷⁰	±20% change
	Manual muscle testing ⁷¹ MDAAT ⁷²	±15% change
Myasthenia gravis	MG composite† ⁷³	
	MG-ADL Score ⁷⁴	±3 points
	Respiratory function, for example, forced vital capacity	±10% change

*At our centre, measurement of first dorsal interosseous is added to the standard six pairs of muscle groups, to better reflect the pattern of weakness in neuropathy.

†Validated.

‡Responsive.

ABC, activities-specific balance confidence; CIDP, chronic inflammatory demyelinating polyneuropathy; CK, creatine kinase; HAQ, health assessment questionnaire; INCAT, inflammatory neuropathy cause and treatment; MCID, minimal clinical indication of change; MDAAT, myositis disease activity assessment tool; MG, myasthenia gravis; MG-ADL, myasthenia gravis activities of daily living; MMN, multifocal motor neuropathy; MRC, Medical Research Council; ONLS, overall neuropathy limitations scale; RODS, rasch-built overall disability scale.

markedly exceeds the 7.5 mg prednisolone (or equivalent) per day for 3 months or longer recognised to impart high risk of fragility fracture, independent of age or sex.³⁰ Second, immobility related to the neuromuscular disability is a further risk factor for osteoporosis. We recommend documenting the absolute risk of major osteoporotic or hip fracture over 10 years using the validated online FRAX Fracture Risk Assessment Tool.³¹ This 10-year fracture risk should be considered alongside the patient's age to determine the need for treatment—lower and upper risk thresholds for each age bracket are provided (of note, the FRAX tool is only validated for people aged between 40 and 90

years; cases of concern outside the validated age range can be discussed with an osteoporosis specialist).^{32 33}

Treatment is advised if a patient's fracture risk is above the upper threshold. Routine measurement of bone mineral density with dual-energy X-ray absorptiometry (DXA) scanning is not always required but should be performed in people whose fracture risk lies between the lower and upper thresholds for their age; it can also be used as a baseline marker to assess treatment response. The FRAX Score can then be recalculated with the bone mineral density: if the new risk score lies above the given intervention threshold for their age, treatment is recommended. If a patient's 10-year risk of fracture falls above the 'very high risk' threshold, referral to an osteoporosis specialist is advised.³²

Because of the potential for underestimating risk in this cohort (as immobility secondary to the neuromuscular disease is often not considered), it is important to look for evidence of vertebral fractures (spinal X-ray or preferably axial MR) if there is a history suggesting fracture, such as unexplained back pain, loss of height or known spinal osteoporosis (figure 4). The finding of a fracture considered to be osteoporotic would trigger consideration of bisphosphonate therapy.

When considering a bisphosphonate for osteoporosis, the subsequent risk of osteonecrosis of the jaw should trigger advice to patients to have a comprehensive and timely dental examination and undergo any required treatment if possible before starting treatment. Dentists may refuse to treat patients who have previously used bisphosphonates, especially if given intravenously or alongside immunosuppression.³⁴

Oral bisphosphonates (alendronic acid, ibandronic acid and risedronate sodium) are recommended in adults if the 10-year probability of osteoporotic fragility fracture is at least 1%, or 'high risk' according to FRAX. Vitamin D and calcium should be supplemented if subnormal on baseline testing.

Intravenous bisphosphonates (ibandronic acid and zoledronic acid) are recommended if the 10-year probability of osteoporotic fragility fracture is at least 10% (eg, in immobile individuals), if the 10-year probability of osteoporotic fragility fracture is at least 1% and the person has difficulty taking oral bisphosphonates (alendronic acid, ibandronic acid or risedronate sodium), or if oral bisphosphonates are otherwise contraindicated or not tolerated. Discussion with rheumatology is advised when fracture risk is greater than 10%, if a fracture occurs while on treatment or if there are any other concerns.

Bone protection should be continued for at least 3 years for zoledronic acid or 5 years for oral bisphosphonates. Fracture risk should then be reassessed with FRAX, with or without DXA as indicated at that point. Longer treatment is recommended if patients are above 75 years old, there is a history of hip or vertebral fracture, there has been a fracture while on

Table 6 Properties and therapeutic indications of oral corticosteroids, relative to hydrocortisone

Drug	GC:MC ratio		General therapeutic indication
Hydrocortisone (S)	1	1	Relatively high mineralocorticoid activity makes it unsuitable for long-term use
Cortisone (S)	0.8	0.8	Similar to hydrocortisone
Prednisolone (I)	4	0.8	High glucocorticoid activity makes it useful for long-term treatment, and as an anti-inflammatory and immunosuppressant
Methylprednisolone (I)	5	Minimal	Anti-inflammatory and immunosuppressive
Dexamethasone (L)	30	Minimal	Anti-inflammatory and immunosuppressive, used especially when water retention is undesirable as it has insignificant mineralocorticoid activity. Long duration of action makes it useful in conditions such as congenital adrenal hyperplasia
Betamethasone (L)	30	Negligible	Anti-inflammatory and immunosuppressive, used especially when water retention is undesirable as it has insignificant mineralocorticoid activity. Long duration of action makes it useful in conditions such as congenital adrenal hyperplasia.

GC, glucocorticoid; I, intermediate acting, biological half-life 18–36 hours; L, long acting, biological half-life 36–54 hours; MC, mineralocorticoid; S, short acting, biological half-life 8–12 hours.

Table 7 Sick-day rules steroid adjustment⁷⁵

Steroid medication	Normal dose	Unwell with fever	COVID-19 (suspected or confirmed)
Prednisolone	3–10 mg/day	5 mg two times per day	10 mg two times per day
Prednisolone	10 mg or more per day	Split dose to two times per day	Split daily dose to two times per day
Hydrocortisone	>10 mg daily	20 mg immediately, then 10 mg 6-hourly	20 mg 6-hourly
Other steroid preparation	N/A	20 mg hydrocortisone immediately, then 10 mg 6-hourly	Hydrocortisone 20 mg 6-hourly

bisphosphonate treatment or if treatment with oral glucocorticoids will be prolonged.

After stopping bone protection, it is important to reassess risk after any new fracture, regardless of when this occurs. If no new fracture occurs, the risk should be reassessed at 18 months to 3 years. Care must be taken not to forget reassessment in young women with significant steroid exposure or other risks. There are insufficient data to recommend bisphosphonate use in pregnancy, and so current guidelines suggest stopping bisphosphonate treatment 3 months before conception.³⁵

Conception, pregnancy and breast feeding

Women of childbearing age require particular consideration when choosing appropriate immunotherapy because of the potential teratogenicity of most drugs and relative immuno-compromise when pregnant. Long-term accumulation of observational data on the use of first-line immunosuppression has allowed for the following recommendations to be made: oral corticosteroids, intravenous immunoglobulin and azathioprine are safe preconception, throughout pregnancy and while breast feeding.^{36–38} Concomitant use of highly effective contraception during treatment and for at least 90 days after stopping treatment is recommended for methotrexate, mycophenolate mofetil and cyclophosphamide (table 4).

Methotrexate should be stopped at least 1 month pre conception, with mycophenolate held 6 weeks in advance. Cyclophosphamide at doses used in treatment of vasculitis results in infertility in women,

especially over the age of 25, and reduced fertility in men. Pretreatment counselling and egg or sperm donation should be considered, if possible, if the clinical situation allows.³⁸

The UK Medicines and Healthcare products Regulatory Agency advised in 2018 that men taking mycophenolate mofetil should use contraception, as the potential risk of genotoxicity on sperm could not be excluded.³⁹ In 2022, the British Society for Rheumatology released updated guidance³⁸ regarding use of immunomodulatory drugs in pregnancy, advising that paternal exposure to mycophenolate mofetil was safe; however, they classed the available evidence as poor quality, and described the recommendation as weak. Clinicians should discuss both sets of guidance, to facilitate an informed decision by the patient.

Vaccinations and infection avoidance

All individuals taking more than 20 mg prednisolone per day for more than 4 weeks or any of the other medications included in this review should be advised to have a single pneumococcal vaccination and an annual influenza vaccination, and not to receive any live vaccinations.^{40–42} Patients who are naïve to varicella zoster virus (VZV) should receive aciclovir or zoster-specific immune globulin in the event of VZV exposure; patients should therefore be advised to inform their treating physician if they are exposed.⁴³

Oral immunosuppression (other than corticosteroids) should be stopped during intercurrent infections, taking into account the risk of cessation and disease recurrence, until the patient recovers from the serious

Table 8 Monitoring in all steroid-sparing agents

When	What
Pretreatment	FBC, U&E, eGFR, LFT, albumin, beta-HCG
Monitoring	Every 2 weeks until dose stable for at least 6 weeks: FBC, U&E, eGFR, LFT, albumin
	Monthly for first 3 months on stable dose: FBC, U&E, LFT, albumin
	Then every 3 months: FBC, U&E, LFT, albumin
Following dose change	Every 2 weeks until dose stable for at least 6 weeks: FBC, U&E, eGFR, LFT, albumin

beta-HCG, beta human chorionic gonadotrophin; eGFR, estimated glomerular filtration rate; FBC, full blood count; LFT, liver function tests; U&E, urea and electrolytes.

Table 9 Actionable events in all steroid-sparing agents

Event	Action
White blood cell count < $3.5 \times 10^9/L$	Withhold until discussion with lead clinician
Neutrophils < $1.6 \times 10^9/L$	
Unexplained eosinophilia > $0.5 \times 10^9/L$	
Platelets < $140 \times 10^9/L$	
Creatinine > 30% above baseline or eGFR < $60 \text{ mL/min/1.73 m}^2$	Withhold until discussion with lead clinician
ALT, AST > 100 IU/L	
Unexplained fall in serum albumin	Withhold until FBC available and discuss with lead clinician
Rash or oral ulceration	
MCV > 105 fL	Check and treat B12, folate, thyroid function. If normal, withhold until discussion with lead clinician
Abnormal bruising or severe sore throat	Withhold until FBC available and discuss with lead clinician

ALT, alanine transaminase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; FBC, full blood count; MCV, mean cell volume; WBC, white blood cell.

infection. The steroid dose should be maintained. It is not recommended that immunosuppression should be routinely stopped preoperatively; steroid dose should be minimised, if possible. Steroid dose should not

Table 10 Characteristics of steroid-sparing agents

Drug	Benefits	Drawbacks
AZA	Relatively rapid onset (3–6 months) Safe in pregnancy Can assess patient concordance with metabolites and neutrophil count	Greater tendency for nephrotoxicity and hepatotoxicity
MMF	Less hepatotoxic Can uptitrate more quickly Better gastrointestinal tolerance	
MTX	Once-weekly dosing	Possible association with fibrosis

AZA, azathioprine; MMF, mycophenolate mofetil; MTX, methotrexate.

be increased perioperatively to pre-emptively avoid adrenal insufficiency.⁴⁴ However, if there is concern that there is a particularly high risk of perioperative or postoperative infection, the individual case should be discussed with the local microbiologists. This also applies to dental procedures.

Treatment: induction and monitoring

The two important elements of treatment induction and maintenance are:

- ▶ Drug efficacy monitoring, which should be disease centred and patient centred.
- ▶ Drug safety screening and monitoring, which should be drug centred and patient centred.

Efficacy monitoring

In neuromuscular disease, treatment efficacy or failure is primarily a clinical decision. There are no reliable serological biomarkers of disease activity (other than creatine kinase, which has some relative responsiveness

Table 11 Potential serious adverse events with cyclophosphamide and prevention recommendations

Adverse reactions	Prevention
Bladder toxicity	1 L prehydration with sodium chloride 0.9% or orally over 1 hour before cyclophosphamide 3 L/day oral fluid intake for 3 days Mesna 200 mg intravenous in 100 mL sodium chloride 0.9% infusion over 30 min before cyclophosphamide Mesna 400 mg PO at 2 hours post cyclophosphamide Mesna 400 mg PO at 6 hours post cyclophosphamide
<i>Pneumocystis jirovecii</i> pneumonia	Cotrimoxazole 480 mg three times a week (care with allergy)
Gastrointestinal disturbance	Cyclizine 50 mg slow intravenous bolus or ondansetron 8 mg slow intravenous bolus 15 min before cyclophosphamide Domperidone 10–20 mg PO three times a day for 3–5 days
Cervical intraepithelial neoplasia	Annual smear for 3 years Follow-up as per national guidelines
Vaccination	Influenza Pneumococcus Avoid live vaccination
Fungal infection	Consider prophylaxis
<i>Staphylococcus aureus</i>	Consider treatment in ANCA-associated vasculitis
Infertility	Counsel Consider cryopreservation if clinically permitted
Osteoporosis	Bisphosphonate+calcium + vitamin D
Tuberculosis	Risk assessment
HBV, HCV, HIV, VZV	Screen pretreatment Treat if indication (specialist discussion)

HBV, hepatitis B virus; HCV, hepatitis C virus; PO, orally; VZV, varicella zoster virus.

Table 12 Cyclophosphamide dose adjustment in chronic renal impairment

Age (years)	Creatinine 150–300 µmol/L	Creatinine 300–500 µmol/L
<60	15 mg/kg/pulse	12.5 mg/kg/pulse
≥60 and <70	12.5 mg/kg/pulse	10 mg/kg/pulse
≥70	10 mg/kg/pulse	7.5 mg/kg/pulse

in myositis, and the erythrocyte sedimentation rate or C-reactive protein in some cases of systemic vasculitis).⁴⁵ To establish objective evidence of clinical change, we recommend using disease-specific and symptom-specific outcome measurements at pretreatment and post-treatment assessments. The concomitant assessment of at least three different measures is advised because sensitivity can vary. [table 5](#) lists some of the tools available.

The minimal clinical indication of change (MCID) is ‘a change that is considered meaningful and worthwhile by the patient such that they would consider repeating the intervention’⁴⁶ and is becoming more popular than a statistically significant difference in chosen outcomes in the clinical trial setting. This principle can be applied to clinimetrically sound, interval, metric-based scales. Taking the MCID into consideration can help interpret the real-life value of the treatment, but overall clinical judgement should also be applied.

Safety screening and monitoring

We have already discussed some of the general immunotherapy-related risks with regard to infection, bone health and woman of childbearing age, but each individual agent has drug-specific risks and particular requirements for screening and monitoring depending on mechanism of action, pharmacodynamics and pharmacokinetics. We will discuss corticosteroid-associated safety screening and monitoring, then the

steroid-sparing agents as a group highlighting some agent-specific issues, followed by cyclophosphamide. Basic common guidance on dosing and monitoring are provided in the Physicians’ Quick Guide but it is important to adjust these according to individual disease severity, comorbidity and potential risk (see online supplemental material).

Corticosteroids

The therapeutic effects of an oral corticosteroid depend on its properties. [Table 6](#) outlines the properties and indications of commonly-used oral corticosteroids. Mineralocorticoids are prescribed to replace deficiencies in hormone concentrations resulting from reduced aldosterone production (eg, in Addison’s disease). Glucocorticoids have four main effects:

- ▶ Anti-inflammatory—inhibiting inflammation by blocking the action of inflammatory mediators (such as prostaglandins).
- ▶ Immunosuppressive—suppressing delayed hypersensitivity reactions (by directly affecting T-lymphocytes).
- ▶ Antiproliferative (anti-mitotic)—inhibiting DNA synthesis and epidermal cell turnover.
- ▶ Vasoconstrictive—inhibiting the action of histamine and other vasoactive mediators, and also directly affecting vascular endothelial cells.

The adverse effects of oral corticosteroids are largely dose related and commonly seen in those on doses of prednisolone 20 mg/day or equivalent. Familiarity with the range of steroid associated adverse effects is very helpful in counselling, reassurance and symptom management in this patient group. They can often be predicted according to the mineralocorticoid properties (which may cause water retention and hypertension) or glucocorticoid properties (which may cause diabetes mellitus and osteoporosis).⁴⁷ People receiving long-term oral corticosteroids (more than 3 weeks’ duration) and those needing frequent courses (three or four per year) are at risk of systemic adverse effects, which are:

Table 13 Audit metrics

Performance (outcome measures)		Safety	
Berg balance score	Change from baseline	Checklist	% complete
MRC sum score		Significant adverse event rate	Number per year
10 m timed walk		Screening blood tests	% complete
I-RODS		Monitoring documentation	Pretreatment bloods % complete
Creatine kinase			Maintenance bloods % compliant
HAQ Score			Actionable events % actioned
Grip strength		Consent	% documented

HAQ, health assessment questionnaire; I-RODS, inflammatory rasch-built overall disability scale; MRC, Medical Research Council.

Table 14 Immunosuppressant dose adjustment in chronic renal impairment

Drug	Accumulates in chronic renal impairment	Potential for nephrotoxicity	Chronic renal impairment (GFR, mL/min/1.73 m ²)		
			Stage III (30–59) Adjustment (% of standard dose)	Stage IV (15–29)	Stage V (<15)
AZA	No	No	Normal	75%–100%	50%–100%
MTX	Yes	Yes	50%	Contraindicated	Contraindicated
MMF	Yes	No	Normal	1 mg two times per day max	1 mg two times per day max
CYC	Yes	Yes	According to age and serum creatinine (table 13)		

AZA, azathioprine; CYC, cyclophosphamide; GFR, glomerular filtration rate; MMF, mycophenolate mofetil; MTX, methotrexate.

- ▶ Endocrine—adrenal insufficiency (fatigue, anorexia and weight loss, abdominal pain, nausea and vomiting, headache, joint pains, dizziness and fever), weight gain and diabetes mellitus (new-onset, or worsening of blood glucose control in existing diabetes mellitus).
- ▶ Gastrointestinal—peptic ulceration with perforation and haemorrhage, especially with a history of gastro-oesophageal reflux disease, increasing age, concomitant non-steroidal anti-inflammatory drugs and anticoagulants, and serious comorbidity (such as advanced cancer).
- ▶ Psychiatric—confusion, irritability, delusions and suicidal thoughts early in treatment and especially with high doses.
- ▶ Musculoskeletal—osteoporosis, proximal myopathy and rarely avascular necrosis of the long bones.
- ▶ Ophthalmic—glaucoma and cataracts.
- ▶ Cardiovascular—hypertension.
- ▶ Skin—thinning of the skin, easy bruising and delayed wound healing.
- ▶ Other—immunosuppression, Cushing's syndrome (usually reversible on withdrawal of treatment) and irreversible growth suppression in children and adolescents.

Corticosteroids may also mask the clinical signs (such as pain) of serious systemic disorders and infections. All patients should carry a steroid card in case of sickness—care providers can navigate to <http://www.nhsforms.co.uk/> for free printing. Careful steroid sick day management should be taught to all patients (table 7), alongside the importance of having adequate supply and not stopping corticosteroid treatment abruptly in order to avoid an adrenal crisis. Advice of regimens for gradual dose reduction are provided in the Physicians' Quick Guide (online supplemental material).

Steroid-sparing agents

Table 8 provides guidance on safety monitoring for commonly used steroid-sparing agents in neuromuscular diseases: azathioprine, methotrexate and mycophenolate.¹⁸ In our department, this is overseen by a clinical nurse specialist via telephone clinics facilitated by the consensus departmental guidance on actionable events and monitoring requirements. This process is supported by the lead clinician—in our experience, it is manageable in brief weekly meetings or via email or telephone

communication when required. In some situations, the patient's primary care provider will accept some shared care responsibility and monitoring blood tests can be performed locally and fed back to the hospital for action if required. However, not all primary care providers can support this approach; some are able to do so during the maintenance phase once treatment induction and dosing is established. The aim of monitoring is to avoid serious adverse events through the identification of a worrying trend or on reaching a threshold as listed in the actionable events box (table 9), which should result in either dose reduction or omission for a period of time, or a switch to an alternative steroid-sparing agent. Clinical reasoning should be applied to each case on an individual basis. Dosing and drug-specific information is provided in the Physicians' Quick Guide (online supplemental material).

Selection of the most appropriate steroid-sparing agent should be patient specific and disease specific. tables 1 and 10 summarise the relative benefits and drawbacks of the different medications.

Cyclophosphamide

The initial treatment of patients with primary systemic vasculitis with generalised or threatened neurological dysfunction should include cyclophosphamide where not contraindicated. Combination therapy with cyclophosphamide and prednisolone is effective in inducing remission,^{48 49} although rituximab is an effective alternative in remission induction and remission maintenance in ANCA-associated vasculitis.⁵⁰ Formal written consent must be used to provide confirmation of informed consent before treatment. table 11 lists potential serious adverse events which should be discussed with patients as part of the informed consent, as well as recommendations to minimise or prevent these complications.

The dose of cyclophosphamide should be tailored to age, renal function and white blood cell count or neutrophil count (table 12 and Physicians' Quick Guide, online supplemental material). The standard dose is 15 mg/kg, but a maximum of 1.5 g should not be exceeded for most inflammatory conditions regardless of weight, and we seldom exceed 1 g per dose. The induction regimen includes a combination of corticosteroids and cyclophosphamide delivered in pulses (up to 10) monitored

for safety with the neutrophil response, renal function and other adverse effects, and tolerance monitored in the individual. Pulses 1–3 should be given 2 weeks apart followed by 3 weekly intervals for pulses 4–10. Depending on tolerance and patient preference, the last four doses can be given orally in tablet form. Clinical follow-up to ensure efficacy is as important as safety monitoring in vasculitis and is recommended monthly for the first 3 months, every 3–6 months for a year and 6–12 monthly for 2–5 years. Clinical monitoring should include the use of disease-specific and symptom-specific objective outcome measurements as stated above. Clinical response is expected within 3–6 months of cyclophosphamide induction. Maintenance therapy should be started within 3 weeks of completing cyclophosphamide treatment (alongside the gradual downtitration of corticosteroids). Azathioprine,⁵¹ methotrexate⁵² and mycophenolate⁵³ can be used in the maintenance phase. Patients who do not tolerate cyclophosphamide can be converted to maintenance immunosuppression earlier. Maintenance immunosuppression for vasculitis should be continued for at least 18 months before considering withdrawal, but probably 2 years at a minimum and possibly 5 years of treatment is generally recommended by rheumatology and nephrology experience.^{54–56} Relapse rates are particularly high (approximately 20% at 2 years) in granulomatosis with polyangiitis.

In the event of a minor relapse, restart prednisolone at 30 mg per day and review the immunosuppressive approach: either optimise current maintenance treatment, or consider a change to an alternative steroid-sparing agent. If a major or life-threatening relapse occurs, then restart cyclophosphamide or consider rituximab in ANCA-associated vasculitis at induction doses alongside oral prednisolone 30 mg daily or intravenous methylprednisolone 1 g per day for 3 days, as long as the maximum lifetime cumulative cyclophosphamide dose of 25 g,⁵⁷ has not been reached. Excessive cyclophosphamide dosing significantly increases the risk of cardiotoxicity in the short-term and haematological malignancy in the long term. In refractory disease, it is important to consider alternative diagnoses and discuss with a specialist with experience in the management of treatment-resistant or relapsing vasculitis.

Treatment change and cessation

Any chosen immunosuppressive agent should be both effective and safe—if there is toxicity or lack of efficacy, the drug dosing or chosen agent should be reviewed. Clinicians also need to consider duration of treatment where there has been a good clinical response and the disease is in remission. The absence of any clinical deterioration over 2–3 years of follow-up while on maintenance therapy is reassuring. However, there are poor data on the natural history of many of these conditions, including the likelihood of long-term remission. If a patient and clinician decide together to stop immunosuppression, close clinical monitoring

should still continue. In our experience, intermittent clinical assessment (every 6–12 months) over 2–3 years after cessation of immunosuppression is reassuring as evidence of clinical stability. If the decision is made to discharge from routine review, patients should be advised how to access clinical assessment in the event of a possible relapse.

GOVERNANCE AND AUDIT

The prescription of immunosuppression is a relatively high-risk area within neurology. These guidelines provide a framework for quality and safety evaluation. Within our practice, we aim to record performance and safety metrics listed in [table 13](#) every 2 years as part of an audit cycle. The introduction of computerised hospital administration and a categorical approach to immunosuppression monitoring can support the easy collection of these data if we input the information in an accessible format. The introduction of a preimmunosuppression checklist document (online supplemental file 9) is currently being trailed in our department.

CONCLUSION

As neurologists, we often use first-line immunosuppressants to treat autoimmune neuromuscular diseases and beyond. We do not intend this as a prescriptive document and acknowledge that individual patient issues will dictate management that may lie outside of these guidelines. Clear documentation of risk associated with any medical decision is essential and doctors have a duty to take reasonable care to ensure that patients are aware of ‘material risks’. We hope that this general, evidence-based, disease-focused approach to first-line immunosuppression will provide a helpful framework from which to make safe and sensible decisions in the clinical environment. The Physicians’ Quick Guide (online supplemental material) provides a summary of the figures and tables from this document. It can be downloaded to be used in real-time in any patient-facing setting; we hope it is useful. Please note that advice may change, notwithstanding global pandemics, and we review and update our guidelines every 2 years, or on an ad hoc basis if a particular issue arises.

Key points

- ▶ Clinicians prescribing immunosuppressive treatments for neuromuscular diseases should be aware of the shared and individual risks and benefits of distinct drug agents as applied to different conditions.
- ▶ Drug selection and counselling should be tailored to the patient and their disease, rather than one-size-fits-all.
- ▶ Patients taking immunosuppressive treatments need close monitoring for both drug efficacy and safety; prescribing clinicians may need to adjust their approach if there is disease progression or toxicity.

Further reading

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