First-line immunosuppression in neuromuscular diseases

MA Foster[1, 3], MP Lunn[2, 3], AS Carr[2, 3]

1. Division of Neurology, National Hospital for Neurology and Neurosurgery, Queen Square, London

2. Centre for Neuromuscular Diseases, National Hospital for Neurology and Neurosurgery, Queen Square, London

3. UCL Queen Square Institute of Neurology, University College London, Queen Square, London

Word count: 4603

References: 75

Tables: 14

Figures: 4

Supplementary material: i) Patient information booklets

ii) Physicians' Quick Guide

iii) Initiation checklist

ABSTRACT

Autoimmune neuromuscular diseases are a common and often treatable cause for peripheral nervous system dysfunction. If not optimally managed they result in meaningful impairments and disability. The aim of the treating neurologist is 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 multi-specialty evidence and expertise with a focus on autoimmune neuromuscular diseases to create guidance on initiation, dosage and monitoring for toxic effects of the commonly used drugs. These include corticosteroids, steroid sparing agents and cyclophosphamide. Efficacy monitoring advice is also provided, 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 cross-over.

INTRODUCTION

Autoimmune myopathies, neuropathies and myasthenic syndromes have differing pathogenesis and diverse clinical presentations.[1–3] Immunosuppressive (generalised suppression of the immune system) and immunomodulatory (supplementation or alteration of the immune response without suppression) treatment is based on the sole or combined use of corticosteroids, intravenous immunoglobulin (IVIg), plasma exchange, cyclophosphamide or rituximab in the acute phase. Oral immunosuppressant steroid-sparing agents (SSAs) are used completely alone, or more commonly in combination with – and then after – corticosteroids, enabling steroid reduction and remission maintenance. Randomised controlled trials of immunosuppression have been completed in Guillain–Barre syndrome,[4] chronic inflammatory demyelinating polyneuropathy,[5] myasthenia gravis,[6] inflammatory myopathies[3] 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 prescription 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, multi-specialty input and consensus expert neuromuscular clinical opinion. Supplementary documents linked to this article can be used to support informed consent of patients, and guide pre-treatment 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.

The aim of this approach is to optimise clinical outcomes and minimise complications as any degree of immunosuppression, albeit with medications in common use, represents a relatively high-risk intervention for the practicing clinical neurologist.

Mechanism of action

Knowledge of drug-specific mechanisms of action informs appropriate selection, usage and the expectations of response, as well as understanding of side-effects, their timely monitoring and when to action a change in treatment (Table 1).

Table 1: Mechanism of action of common immunomodulatory agents

Drug	**Mechanism of action**	**Immune consequences**
Corticosteroids	Inhibition of gene transcription for secretion of inflammatory cytokines	Reduction of leukocyte 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; inhibition of purine synthesis	Specific immune cell targets unknown

Mycophenolate	Blocks *de novo* purine synthesis	Anti-lymphocyte (T- and B-cell) action. Less toxicity 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). Pathogenic antibodies reduced and disruption of other roles of B-cells (e.g. as antigen-presenting cells) in the immune system.

APPROACH TO IMMUNOSUPPRESSION IN NEUROMUSCULAR DISEASES

We use a clinical, patient-centred approach to the selection and use of immunosuppressant medications. Within broad boundaries, the dose and duration of treatment is largely dependent on clinical response, and there should always be stopping criteria set before starting. A systematic approach to patient assessment for each medication is recommended 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 the establishment of eligibility, practising fully-informed consent procedures, appropriate treatment induction, maintenance monitoring for safety and efficacy, and regular review to consider if ongoing treatment is still required (Figure 1).

Eligibility

The diagnosis of an autoimmune neuromuscular disease should always be made as thoroughly as possible, with appropriate and ample laboratory support before

treatment is considered. This includes a tissue diagnosis where it is possible and relevant, especially in vasculitis or where first-line response has not been as expected. Once treatment is initiated, retrospectively collecting pathological data with diagnostic relevance is virtually impossible. The diagnosis and supporting investigations should be clearly documented, preferably alongside diagnostic criteria where available. The diagnostic approaches to the conditions mentioned in this article have been discussed in previous publications in this journal.[10–14]

Treatment choice is dependent on the disease; Table 2 provides a simplified summary of preferential drug choice, developed by neuromuscular consultants in our department. Careful consideration of patient comorbidities and disease severity is essential.

Table 2: Immunotherapy choices in inflammatory neuromuscular diseases

	Steroids	**IVIg/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
PM	1	2	2	2	3	*	*
DM	1	2	2	2	3	*	*
MG	1	cr > m	2 (m)	3 (m)	2 (m)	*	1

AZA: azathioprine; CIDP: chronic inflammatory demyelinating polyneuropathy; CYC: cyclophosphamide; DM: dermatomyositis; GBS: Guillain–Barré syndrome; MG: myasthenia gravis; MMF: mycophenolate mofetil; MMN: multifocal motor neuropathy; MTX: methotrexate; PLEX: plasma exchange; PM: polymyositis; SCIg: subcutaneous immunoglobulin; 1: first-line; 2: second-line; 3: third-line; * may consider in individual cases; cr: treatment of myasthenic crisis; m: maintenance treatment; no - not recommended.

Informed consent

Prior to 2020, 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. A serious adverse event as defined by the World Health Organisation is 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 (Supplement i). Each booklet outlines, in clear and simple language, basic information about the drug, why it is used, how it is taken, what the possible side effects might be and the approximate frequency of their occurrence. We also highlight the safety measures in place to minimize risk, including monitoring and prophylaxis in certain situations. We discuss alternative options and expected outcome or prognosis if the individual chooses not to take this particular medication. Some basic references are given with advice on where further patient-appropriate information can be found.

However, the Montgomery judgment 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 risk in the individual

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

Pre-treatment 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 prior to treatment initiation in accordance to Q-RISK2 or other population-specific, validated risk calculator.[17] The need to consider current and future fertility and conception, breast-feeding (Table 6) and other physiological states, such as bone health (Figure 4), is also important. The rheumatology literature strongly recommends the following as minimum pre-treatment screening,[18] with actionable events outlined in Table 3:

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

Table 3: Actionable events in pre-immunosuppression co-morbidity screening

Situation	**Recommendation**
Suspicion of parenchymal lung disease	Smoking-cessation advice Lung function tests CXR +/- high resolution CT chest Consider referral to a respiratory physician
HIV, HBV and HCV	Consider anti-viral treatment prior to immuno-suppression (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 4)
Cardiovascular risk	Primary prevention pre-treatment
Previous malignancy	Not an absolute contraindication Routine population screening recommended

ALT: alanine transaminase; AST: aspartate aminotransferase; AZA: azathioprine; CXR: chest X-ray; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; MMF: mycophenolate mofetil; MTX: methotrexate

Table 4: Immunosuppressant dose adjustment in chronic renal impairment

Drug	**Accumulates in CRI**	**Potential for nephrotoxicity**	**Chronic renal impairment (GFR, mL/min/1.73m^2)**		
			Stage III (30-59)	Stage IV (15-29)	Stage V (<15)
			Adjustment (% of standard dose)		
AZA	no	no	normal	75-100%	50-100%
MTX	yes	yes	50%	CI	CI
MMF	yes	no	normal	1 mg BD max	1 mg BD max

CYC	yes	yes	according to age and creatinine *(Table 13)*

AZA: azathioprine; CI: contraindicated; CRI: chronic renal impairment; CYC: cyclophosphamide; GFR: glomerular filtration rate; MMF: mycophenolate mofetil; MTX: methotrexate

Tuberculosis risk

The risk of re-activation of latent TB should be considered in those receiving prednisolone at a dose greater than 15 mg/day (or equivalent) for more than six weeks, those on tumour necrosis factor-α (TNF-α) inhibitors, and those on vasculitis treatment (combination therapy with pulsed cyclophosphamide and high dose steroids).[19] An algorithm for assessing TB risk is shown in Figure 2. TB treatment should always be given under the care of an experienced respiratory physician.

Pneumocystis jirovecii pneumonia (PJP) prophylaxis

Pneumocystis jirovecii (previously known as *Pneumocystis carinii*) is an obligate extracellular fungus which infects the majority of children during childhood and is latent in up to 70% of non-HIV infected adults. Reactivation causing PJP has a mortality rate of 17%, rising to more than 50% in the critically ill.[20] Data to support PJP prophylaxis in all patients on high-dose corticosteroids (20mg or more of prednisolone for four or more weeks) are weak and based on a historical, retrospective case series of 116 non-HIV infected patients over a seven-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 PJP is 1.9%[22], and routine PJP prophylaxis is not advised in any current UK rheumatology guidelines. In acute leukaemia, solid organ transplant and stem-cell transplantation PJP occurs in 6.2% of patients without prophylaxis and there is an 85% reduction in infection rates with prophylaxis; this is the basis for PJP prophylaxis in national haemato-oncology guidelines.[23,24] Other specific risk factors beyond corticosteroid use that increase risk of PJP include a CD4 count below 200 cells/mm^3, anti-neutrophil 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 PJP prophylaxis only when prolonged corticosteroid treatment coincides with another significant PJP risk factor.[28]

We recommend prophylaxis with co-trimoxazole 960 mg three times a week for any patient on greater than 20 mg prednisolone for more than four weeks in combination with any of: concomitant HIV infection; age above 80 years; underlying lung disease; previous PJP; 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 steroids and cyclophosphamide are followed by an SSA). In addition, if a patient has a total lymphocyte count of less than 600 cells/mm^3 at baseline, and a course of prednisolone of greater than 15 mg daily is planned for at least three months, their CD4 count should be measured one month into treatment and prophylaxis recommended if the CD4 count is below 200 cells/mm^3.[21,26,28] The advice is summarised in Figure 3.

Prophylaxis should be continued for as long as steroids are taken. Reactivation of infection must be balanced against the side-effect profile of prophylaxis; for co-trimoxazole, this includes non-fatal adverse reactions such as rash, gastrointestinal symptoms, *Clostridium 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 co-trimoxazole in combination increase the risk of bone-marrow failure. Inappropriate antibiotic use adds to the burden of antimicrobial resistance in PJP.[29]

The alternatives to co-trimoxazole, 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. Firstly, the typical steroid dose used in neuromuscular disease markedly exceeds the 7.5 mg prednisolone (or equivalent) per day for three months or longer recognised to impart high risk of fragility fracture, independent of age or sex.[30] Secondly, immobility related to the neuromuscular disability is a further risk factor for osteoporosis. We recommend documentation of 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]

If fracture risk lies above the upper threshold, treatment is advised. Routine measurement of bone mineral density (BMD) 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 BMD: 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 underestimation of 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 MRI) if there is a history suggestive of 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 before initiation of therapy if possible. Dentists may refuse to provide treatment to patients with previous exposure to 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 sub-normal 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% (for example 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 whilst on treatment, or if there are any other concerns.

Bone protection should be continued for at least three years for zolendronic acid, or five 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 bisphosphonate treatment, or if treatment with oral glucocorticoids will be prolonged.

Once bone protection is discontinued 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. As data are insufficient to recommend bisphosphonate use in pregnancy, current guidelines

suggest cessation of bisphosphonate treatment three months in advance of 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, IVIg and azathioprine are safe pre-conception, throughout pregnancy and whilst breast-feeding. [36–38] Concomitant use of highly-effective contraception during treatment and for at least 90 days after treatment cessation is recommended for methotrexate, mycophenolate and cyclophosphamide (Table 5).

Table 5: Immunosuppression safety in pregnancy and breast feeding

	Peri-conception	**T1**	**T2/T3**	**Breast-feeding**	**Paternal exposure**
Prednisolone[36]	yes	yes	yes	yes	yes
IVMP[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[a]	no[a]	no	no
IVIg[37,38]	yes	yes	yes	yes	yes[b]

Rituximab[7,38]	consider stopping at conception[c]	severe disease if no alternatives[c]	severe disease if no alternatives[d]	yes[b]	yes[b]

AZA: azathioprine; CYC: cyclophosphamide; IVIg: intravenous immunoglobulin; IVMP: intravenous methylprednisolone; MMF: mycophenolate mofetil; MTX: methotrexate; [a] only consider in severe life or organ-threatening maternal disease; [b] Limited data available; [c] can consider in severe maternal disease if no pregnancy-compatible alternatives available; [d] if used in third trimester, avoid live vaccinations in infant until six months of age

Methotrexate should be ceased at least one month pre-conception, with mycophenolate held six 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. Pre-treatment counselling and egg or sperm donation should be considered if possible, and if the clinical situation allows.[38]

The MHRA 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 guidance[38] regarding use of immunomodulatory drugs in pregnancy, advising that paternal expose to MMF 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 on greater than 20 mg prednisolone per day for more than four weeks or any of the other medications included in this review should be advised to have a single pneumococcal vaccination and an annual flu 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 discontinued during inter-current infections, taking into account the risk of cessation and disease recurrence, until the patient recovers from the serious infection. The steroid dose should be maintained. It is not recommended that immunosuppression should be routinely stopped pre-operatively; steroid dose should be minimised, if possible. Steroid dose should not be increased peri-operatively to pre-emptively avoid adrenal insufficiency.[44] However, if there is concern that there is a particularly high risk of peri-operative or post-operative 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- and patient-centred.
- drug safety screening and monitoring, which should be drug- and patient-centred

<u>Efficacy monitoring</u>

Treatment efficacy or failure is primarily a clinical decision in neuromuscular disease. There are no reliable serological biomarkers of disease activity (other than creatine kinase, which has some relative responsiveness in myositis, and the ESR/CRP in

some cases of systemic vasculitis).[45] To establish objective evidence of clinical change, the use of disease- and symptom-specific outcome measurements is recommended at pre- and post-treatment assessments. The concomitant assessment of at least three different measures is advised because sensitivity can vary. Table 6 lists some of the tools available.

Table 6: Disease-specific outcome measures in autoimmune neuromuscular diseases

Condition	**Established disability measure**	**MCID**
Chronic inflammatory demyelinating polyneuropathy	MRC sum score†[46]	+/- 2 points
	CIDP-RODS*[47,48]	+/- 4 points (logit scale)
	Vigorimeter (kPa)**[49]	+/- 8 kPa
	10m timed walk (seconds)[50]	+/- 28% change
	ONLS[48,51]	
Other neuropathy/ neuromyotonia	INCAT *[52]	+/-1 point
	Berg balance scale*[50]	+/- 8 points
	ABC balance score*[53]	<50%: low function
	Tremor scale*[54]	
	Myotonia behaviour scale*[55]	
Multifocal motor neuropathy	MRC sum score†[46]	+/- 2 points
	Vigorimeter (kPa)**[49]	+/- 8 kPa
	MMN-RODS*[56]	+/- 4 points (logit scale)
	ONLS[48,51]	
Inflammatory myopathy	MRC sum score†[46]	+/- 2 points

	Timed up and go 3 m walk (seconds)[57]	
	CK	+/- 30% change
	HAQ score*[58]	+/- 15% change
	Physician global activity assessment[59]	+/- 20% change
	Patient/parent global activity assessment[59]	+/- 20% change
	Manual muscle testing (MMT)[60]	+/- 15% change
	MDAAT[61]	
Myasthenia gravis	MG composite*[62]	
	MG-ADL score[63]	+/- 3 points
	Respiratory function, e.g. forced vital capacity	+/- 10% change

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

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’[64] 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 child-bearing 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 SSAs 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 adjustment according to individual disease severity, comorbidity and potential risk should always be considered (see supplementary material).

Corticosteroids

The therapeutic effects of an oral corticosteroid depend on its properties. Mineralocorticoids are prescribed to replace deficiencies in hormone levels resulting from reduced aldosterone production (for example 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);
- Anti-proliferative (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.

Table 7: 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; MC: mineralocorticoid; S: short acting, biological half-life 8-12 hours; I: intermediate acting, biological half-life 18-36 hours; L: long acting, biological half-life 36-54 hours

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).[65] People receiving long-term oral corticosteroids (more

than three weeks' duration) and those needing frequent courses (three or four per year) are at risk of systemic adverse effects, which are:

- 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. Free printing is available from http://www.nhsforms.co.uk/. Careful steroid sick day management should be taught to all patients (Table 8), 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 (supplementary material).

Table 8: Sick-day rules steroid adjustment[66]

Steroid medication	**Normal dose**	**Unwell with fever**	**COVID-19 (suspected or confirmed)**
Prednisolone	3-10 mg/day	5 mg BD	10 mg BD
Prednisolone	10 mg or more per day	Split dose to BD	Split daily dose to BD
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

Steroid-sparing agents

Table 9 provides guidance on safety monitoring for commonly-used SSAs 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 10), which should result in either dose reduction or omission for a period of time, or a switch to an alternative SSA. Clinical reasoning should be applied to each case on an individual basis. Dosing and drug-specific information is provided in the Physicians' Quick Guide (supplementary material).

Table 9: Monitoring in all SSAs

When	**What**
Pre-treatment	FBC, U&E, eGFR, LFT, albumin, beta-HCG
Monitoring	Every two weeks until dose stable for at least six weeks: FBC, U&E, eGFR, LFT, albumin
	Monthly for first three months on stable dose: FBC, U&E, LFT, albumin
	Then every three months: FBC, U&E, LFT, albumin
Following dose change	Every two weeks until dose stable for at least six 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 10: Actionable events in all SSAs

Event	**Action**
WBC count < 3.5 $x10^9$/L	Withhold until discussion with lead clinician
Neutrophils < 1.6 $x10^9$/L	

Unexplained eosinophilia > 0.5 x10^9/L	
Platelets < 140 x10^9/L	
Creatinine > 30% above baseline or eGFR < 60 ml/min/1.73 m^2	
ALT, AST > 100 IU/L	
Unexplained fall in serum albumin	
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

Selection of the most appropriate SSA should be patient- and disease-specific.

Relative benefits and drawbacks of the different medications are summarised in

Table 1 and Table 11.

Table 11: Characteristics of SSAs

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 up-titrate more quickly Better gastrointestinal tolerance	
MTX	Once-weekly dosing	Possible association with fibrosis

AZA: azathioprine; MMF: mycophenolate mofetil; MTX: methotrexate

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,[67,68] although rituximab is an effective alternative in remission induction and remission maintenance in ANCA-associated vasculitis.[69] Formal written consent must be used to provide confirmation of informed consent prior to treatment. Table 12 lists potential serious adverse events which should be discussed with patients as part of the informed consent. Recommendations to minimise or prevent these complications are also provided.

Table 12: 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 prior to cyclophosphamide 3 L/day oral fluid intake for 3 days Mesna 200 mg IV in 100ml sodium chloride 0.9% infusion over 30 minutes before cyclophosphamide Mesna 400 mg PO at 2 hours post cyclophosphamide Mesna 400 mg PO at 6 hours post cyclophosphamide
Pneumocystis jirovecii pneumonia	Co-trimoxazole 480 mg three times per week (care with allergy)
Gastrointestinal disturbance	Cyclizine 50 mg slow IV bolus or ondansetron 8 mg slow IV bolus 15 minutes before cyclophosphamide Domperidone 10-20 mg PO TDS 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
Staphylococcus aureus	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 pre-treatment Treat if indication (specialist discussion)

HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; VZV: varicella zoster virus

Table 13: 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

The dose of cyclophosphamide should be tailored to age, renal function and white blood cell count or neutrophil count (Table 13 and Physicians' Quick Guide, supplementary 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 to 3 should be given two weeks apart followed by three-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 three months, every 3–6 months for a year and 6–12 monthly for 2–5 years. Clinical monitoring should include the use of disease- and symptom-specific objective outcome measurements as stated above. Clinical response is expected within 3–6 months of cyclophosphamide induction. Maintenance therapy should be commenced within three weeks of completion of cyclophosphamide treatment (alongside the gradual down-titration of corticosteroids). Azathioprine,[70] methotrexate[71] and mycophenolate[72] 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 two years at a minimum and possibly five years of treatment is generally recommended by rheumatology and nephrology experience.[73–75] Relapse rates are particularly high (approximately 20% at two years) in granulomatosis with polyangiitis.

In the event of a minor relapse, restart prednisolone 30 mg per day and either optimise current maintenance immunosuppression or consider a change to an alternative SSA. 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[69] has not been reached. Excessive cyclophosphamide dosing

significantly increases risk of cardiotoxicity in the short term and haematological malignancy in the longer 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. An absence of any clinical deterioration over 2–3 years of follow-up whilst 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 the experience of the authors, 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 14 every two 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 pre-immunosuppression checklist document (supplement 3) is currently being trailed in our department.

Table 14: 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	Pre-treatment bloods % complete
Creatine kinase			Maintenance bloods % compliant
HAQ score			Actionable events % actioned
Grip strength		Consent	% documented

CONCLUSION

As neurologists we often use first-line immunosuppressants in the treatment of autoimmune neuromuscular diseases and beyond. We do not intend this as a prescriptive document and acknowledge that individual patient issues will dictate management which 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 approached 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 (supplementary 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 two years, or on an ad-hoc basis if a particular issue arises.

CONTRIBUTORSHIP

MAF prepared the first draft of the manuscript. MPL and ASC developed the topic for the article. All authors contributed to manuscript revisions, and all authors read and approved the submitted version.

ACKNOWLEDGEMENTS

We acknowledge the multi-specialty input from our colleagues at University College London Hospitals NHS Foundation Trust, including in rheumatology (Dr Emon Khan), microbiology (Dr Carmel Curtis) and pharmacy (Sheetal Sumaria), as well as continued clinical feedback from the consultant body of the Centre for Neuromuscular Diseases at the National Hospital for Neurology & Neurosurgery.

MPL and ASC are supported by the UCLH NHS Foundation Trust Biomedical Research Centre.

COMPETING INTERESTS

The authors declare no competing interests relevant to this article.

FUNDING

MAF is supported by a grant from the MRC (MR/S026088/1). MPL and ASC are supported by the UCLH Biomedical Research Centre.

ETHICAL APPROVAL

Not applicable.

DATA SHARING

Not applicable.

REFERENCES

1. Kieseier BC, Mathey EK, Sommer C, et al. Immune-mediated neuropathies. *Nat Rev Dis Primers* 2018; 4: 31.
2. Verschuuren J, Strijbos E, Vincent A. Neuromuscular junction disorders. In: *Handbook of Clinical Neurology*. Elsevier, 2016, pp. 447–466.
3. Selva-O'Callaghan A, Pinal-Fernandez I, Trallero-Araguás E, et al. Classification and management of adult inflammatory myopathies. *Lancet Neurol* 2018; 17: 816–828.
4. Verboon C, Van Doorn PA, Jacobs BC. Treatment dilemmas in Guillain-Barré syndrome. *J Neurol Neurosurg Psychiatry* 2017; 88: 346–352.
5. Lehmann HC, Burke D, Kuwabara S. Chronic inflammatory demyelinating polyneuropathy: Update on diagnosis, immunopathogenesis and treatment. *J Neurol Neurosurg Psychiatry* 2019; 90: 981–987.
6. Farmakidis C, Pasnoor M, Dimachkie MM, et al. Treatment of Myasthenia Gravis. *Neurol Clin* 2018; 36: 311–337.
7. Whittam DH, Tallantyre EC, Jolles S, et al. Rituximab in neurological disease: principles, evidence and practice. *Pract Neurol* 2019; 19: 5–20.
8. McWilliam M, Khan U. Azathioprine and the neurologist. *Pract Neurol* 2020; 20: 69–74.
9. Osman C, Jennings R, El-Ghariani K, et al. Plasma exchange in neurological disease. *Pract Neurol* 2020; 20: 92–101.

10. Chevrel G, Goebels N, Hohlfeld R. Myositis Diagnosis and Management. *Pract Neurol* 2002; 2: 4–11.
11. Fehmi J, Bellanti R, Misbah SA, et al. Treatment of CIDP. *Pract Neurol* 2023; 23: 46–53.
12. Willison H, Mills K. Multifocal Motor Neuropathy. *Pract Neurol* 2002; 2: 298–301.
13. Marsh EA, Davies LM, Llewelyn JG. How to recognise and treat peripheral nervous system vasculitis. *Pract Neurol* 2013; 13: 408–411.
14. Sussman J, Farrugia ME, Maddison P, et al. Myasthenia gravis: Association of British Neurologists' management guidelines. *Pract Neurol* 2015; 15: 199–206.
15. GMC. *Guidance on professional standards and ethics for doctors: Decision making and consent*, www.gmc-uk.org/guidance. (2020).
16. WHO. *International drug monitoring: the role of national centres. Report of a WHO meeting.* Geneva, 1972.
17. Hippisley-Cox J, Coupland C, Vinogradova Y, et al. Predicting cardiovascular risk in England and Wales: Prospective derivation and validation of QRISK2. *BMJ* 2008; 336: 1475–1482.
18. Ledingham J, Gullick N, Irving K, et al. BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. *Rheumatology* 2017; 56: 865–868.
19. Centers for Disease Control and Prevention. *Latent Tuberculosis Infection: A Guide for Primary Health Care Providers*. 2020.
20. Walzer PD, Evans HER, Copas AJ, et al. Early predictors of mortality from Pneumocystis jirovecii pneumonia in HIV-infected patients: 1985-2006. *Clinical Infectious Diseases* 2008; 46: 625–633.
21. Yale SH, Limper AH. Pneumocystis carinii pneumonia in patients without acquired immunodeficiency syndrome: associated illness and prior corticosteroid therapy. *Mayo Clin Proc* 1996; 71: 5–13.
22. Gøtzsche PC, Johansen HK. Short-term low-dose corticosteroids vs placebo and nonsteroidal antiinflammatory drugs in rheumatoid arthritis. *Cochrane Database of Systematic Reviews*; 2005. Epub ahead of print 24 January 2005. DOI: 10.1002/14651858.cd000189.pub2.
23. Stern A, Green H, Paul M, et al. Prophylaxis for Pneumocystis pneumonia (PCP) in non-HIV immunocompromised patients. *Cochrane Database of Systematic Reviews*. Epub ahead of print 1 October 2014. DOI: 10.1002/14651858.CD005590.pub3.
24. Cooley L, Dendle C, Wolf J, et al. Consensus guidelines for diagnosis, prophylaxis and management of Pneumocystis jirovecii pneumonia in patients with haematological and solid malignancies, 2014. *Intern Med J* 2014; 44: 1350–1363.
25. Ognibene FP, Shelhamer JH, Hoffman GS, et al. Pneumocystis carinii pneumonia: a major complication of immunosuppressive therapy in patients with Wegener's granulomatosis. *Am J Respir Crit Care Med* 1995; 151: 795–9.

26. Rodriguez M, Fishman JA. Prevention of infection due to Pneumocystis spp. in human immunodeficiency virus-negative immunocompromised patients. *Clin Microbiol Rev* 2004; 17: 770–82.

27. Strangfeld A, Eveslage M, Schneider M, et al. Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient? *Ann Rheum Dis* 2011; 70: 1914–1920.

28. Sowden E, Carmichael AJ. Autoimmune inflammatory disorders, systemic corticosteroids and pneumocystis pneumonia: a strategy for prevention. *BMC Infect Dis* 2004; 4: 42.

29. Huang L, Crothers K, Atzori C, et al. Dihydropteroate synthase gene mutations in Pneumocystis and sulfa resistance. *Emerg Infect Dis* 2004; 10: 1721–1728.

30. van Staa TP, Leufkens HG, Abenhaim L, et al. Oral corticosteroids and fracture risk: relationship to daily and cumulative doses. *Rheumatology* 2000; 39: 1383–9.

31. Kanis JA, Oden A, Johansson H, et al. FRAX® and its applications to clinical practice. *Bone* 2009; 44: 734–743.

32. National Osteoporosis Guideline Group, https://www.nogg.org.uk/full-guideline (accessed 17 January 2023).

33. McCloskey E, Kanis JA, Johansson H, et al. FRAX-based assessment and intervention thresholds--an exploration of thresholds in women aged 50 years and older in the UK. *Osteoporosis International* 2015; 26: 2091–2099.

34. Woo S bin, Hellstein JW, Kalmar JR. Bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med* 2006; 144: 753–761.

35. Schreiber K, Frishman M, Russell MD, et al. British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: comorbidity medications used in rheumatology practice. *Rheumatology*. Epub ahead of print 2 November 2022. DOI: 10.1093/RHEUMATOLOGY/KEAC552.

36. Hoes JN, Jacobs JWG, Boers M, et al. EULAR evidence-based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. *Ann Rheum Dis* 2007; 66: 1560–1567.

37. Clark AL, Gall SA. Clinical uses of intravenous immunoglobulin in pregnancy. *Am J Obstet Gynecol* 1997; 176: 241–253.

38. Russell MD, Dey M, Flint J, et al. British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids. *Rheumatology*. Epub ahead of print 2 November 2022. DOI: 10.1093/RHEUMATOLOGY/KEAC551.

39. MHRA. Mycophenolate mofetil, mycophenolic acid: updated contraception advice for male patients. *Drug Safety Update*; 11.

40. Public Health England. *Immunisation against infectious disease - chapter 7: immunisation of immunocompromised individuals*. 2020.

41. Public Health England. *Immunisation against infectious disease - chapter 19: influenza*. 2020.

42. Public Health England. *Immunisation against infectious disease - chapter 25: pneumoccocal*. 2020.

43. Public Health England. *Updated guidelines on post exposure prophylaxis (PEP) for varicella/shingles*. 2019.

44. Liu MM, Reidy AB, Saatee S, et al. Perioperative Steroid Management: Approaches Based on Current Evidence. *Anesthesiology* 2017; 127: 166–172.

45. Keh RYS, Shah S, Lilleker JB, et al. Pragmatic guide to peripheral nerve disease and the role of clinical biomarkers. *Pract Neurol*. Epub ahead of print 18 July 2022. DOI: 10.1136/PN-2022-003438.

46. Kleyweg RP, Van Der Meché FGA, Schmitz PIM. Interobserver agreement in the assessment of muscle strength and functional abilities in Guillain-Barré syndrome. *Muscle Nerve* 1991; 14: 1103–1109.

47. Draak THP, Gorson KC, Vanhoutte EK, et al. Correlation of the patient's reported outcome Inflammatory-RODS with an objective metric in immune-mediated neuropathies. *Eur J Neurol* 2016; 23: 1248–1253.

48. Draak THP, Vanhoutte EK, van Nes SI, et al. Changing outcome in inflammatory neuropathies: Rasch-comparative responsiveness. *Neurology* 2014; 83: 2124–32.

49. Vanhoutte EK, Latov N, Deng C, et al. Vigorimeter grip strength in CIDP: A responsive tool that rapidly measures the effect of IVIG - the ICE study. *Eur J Neurol* 2013; 20: 748–755.

50. Telenius EW, Engedal K, Bergland A. Inter-rater reliability of the Berg Balance Scale, 30 s chair stand test and 6 m walking test, and construct validity of the Berg Balance Scale in nursing home residents with mild-to-moderate dementia. *BMJ Open* 2015; 5: e008321.

51. Graham RC, Hughes RAC. A modified peripheral neuropathy scale: the Overall Neuropathy Limitations Scale. *J Neurol Neurosurg Psychiatry* 2006; 77: 973–6.

52. Merkies ISJ, Schmitz PIM, van der Meché FG, et al. Psychometric evaluation of a new sensory scale in immune-mediated polyneuropathies. *Neurology* 2000; 54: 943–9.

53. Powell LE, Myers AM. The Activities-specific Balance Confidence (ABC) Scale. *The Journals of Gerontology: Series A* 1995; 50A: M28-34.

54. Elble R, Comella C, Fahn S, et al. Reliability of a new scale for essential tremor. *Movement Disorders* 2012; 27: 1567–1569.

55. Hammarén E, Kjellby-Wendt G, Lindberg C. Quantification of mobility impairment and self-assessment of stiffness in patients with myotonia congenita by the physiotherapist. *Neuromuscular Disorders* 2005; 15: 610–617.

56. Vanhoutte EK, Faber CG, Van Nes SI, et al. Rasch-built Overall Disability Scale for Multifocal motor neuropathy (MMN-RODS©). *Journal of the Peripheral Nervous System* 2015; 20: 296–305.

57. Podsiadlo D, Richardson S. The Timed “Up & Go”: A Test of Basic Functional Mobility for Frail Elderly Persons. *J Am Geriatr Soc* 1991; 39: 142–148.

58. Fries JF, Spitz P, Kraines RG, et al. Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980; 23: 137–145.

59. Rider LG, Feldman BM, Perez MD, et al. Development of validated disease activity and damage indices for the juvenile idiopathic inflammatory myopathies. I. Physician, parent, and patient global assessments. *Arthritis Rheum* 1997; 40: 1976–1983.

60. Rider LG, Koziol D, Giannini EH, et al. Validation of manual muscle testing and a subset of eight muscles for adult and juvenile idiopathic inflammatory myopathies. *Arthritis Care Res (Hoboken)* 2010; 62: 465–472.

61. Sultan SM, Allen E, Oddis C V., et al. Reliability and validity of the myositis disease activity assessment tool. *Arthritis Rheum* 2008; 58: 3593–3599.

62. Barnett C, Merkies ISJ, Katzberg H, et al. Psychometric Properties of the Quantitative Myasthenia Gravis Score and the Myasthenia Gravis Composite Scale. *J Neuromuscul Dis* 2015; 2: 301–311.

63. Muppidi S, Wolfe GI, Conaway M, et al. MG-ADL: Still a relevant outcome measure. *Muscle Nerve* 2011; 44: 727–731.

64. Vanhoutte EK, Faber CG, Merkies ISJ. 196th ENMC international workshop: Outcome measures in inflammatory peripheral neuropathies 8-10 February 2013, Naarden, The Netherlands. *Neuromuscular Disorders* 2013; 23: 924–933.

65. Meikle AW, Tyler FH. Potency and duration of action of glucocorticoids: effects of hydrocortisone, prednisone and dexamethasone on human pituitary-adrenal function. *Am J Med* 1977; 63: 200–207.

66. Society for Endocrinology. Steroid Sick Day Rules. DOI: 10.1111/anae.14963.

67. Fauci AS, Katz P, Haynes BF, et al. Cyclophosphamide Therapy of Severe Systemic Necrotizing Vasculitis. *New England Journal of Medicine* 1979; 301: 235–238.

68. Collins MP, Dyck PJB, Gronseth GS, et al. Peripheral Nerve Society Guideline on the classification, diagnosis, investigation, and immunosuppressive therapy of non-systemic vasculitic neuropathy: executive summary. *Journal of the Peripheral Nervous System* 2010; 15: 176–184.

69. Ntatsaki E, Carruthers D, Chakravarty K, et al. Guidelines BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis. *Rheumatology* 2014; 53: 2306–2309.

70. Jayne DRW, Rasmussen N, Andrassy K, et al. A Randomized Trial of Maintenance Therapy for Vasculitis Associated with Antineutrophil Cytoplasmic Autoantibodies. *New England Journal of Medicine* 2003; 349: 36–44.

71. De Groot K, Rasmussen N, Bacon PA, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early

systemic antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* 2005; 52: 2461–2469.

72. Hiemstra TF, Walsh M, Mahr A, et al. Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: A randomized controlled trial. *JAMA* 2010; 304: 2381–2388.
73. Sanders JSF, de Joode AAE, Desevaux RG, et al. Extended versus standard azathioprine maintenance therapy in newly diagnosed proteinase-3 anti-neutrophil cytoplasmic antibody-associated vasculitis patients who remain cytoplasmic anti-neutrophil cytoplasmic antibody-positive after induction of remission: a randomized clinical trial. *Nephrology, Dialysis, Transplantation* 2016; 31: 1453–1459.
74. Karras A, Pagnoux C, Haubitz M, et al. Randomised controlled trial of prolonged treatment in the remission phase of ANCA-associated vasculitis. *Ann Rheum Dis* 2017; 76: 1662–1668.
75. Charles P, Perrodeau É, Samson M, et al. Long-Term Rituximab Use to Maintain Remission of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis: A Randomized Trial. *Ann Intern Med* 2020; 173: 179–188.

FIGURES

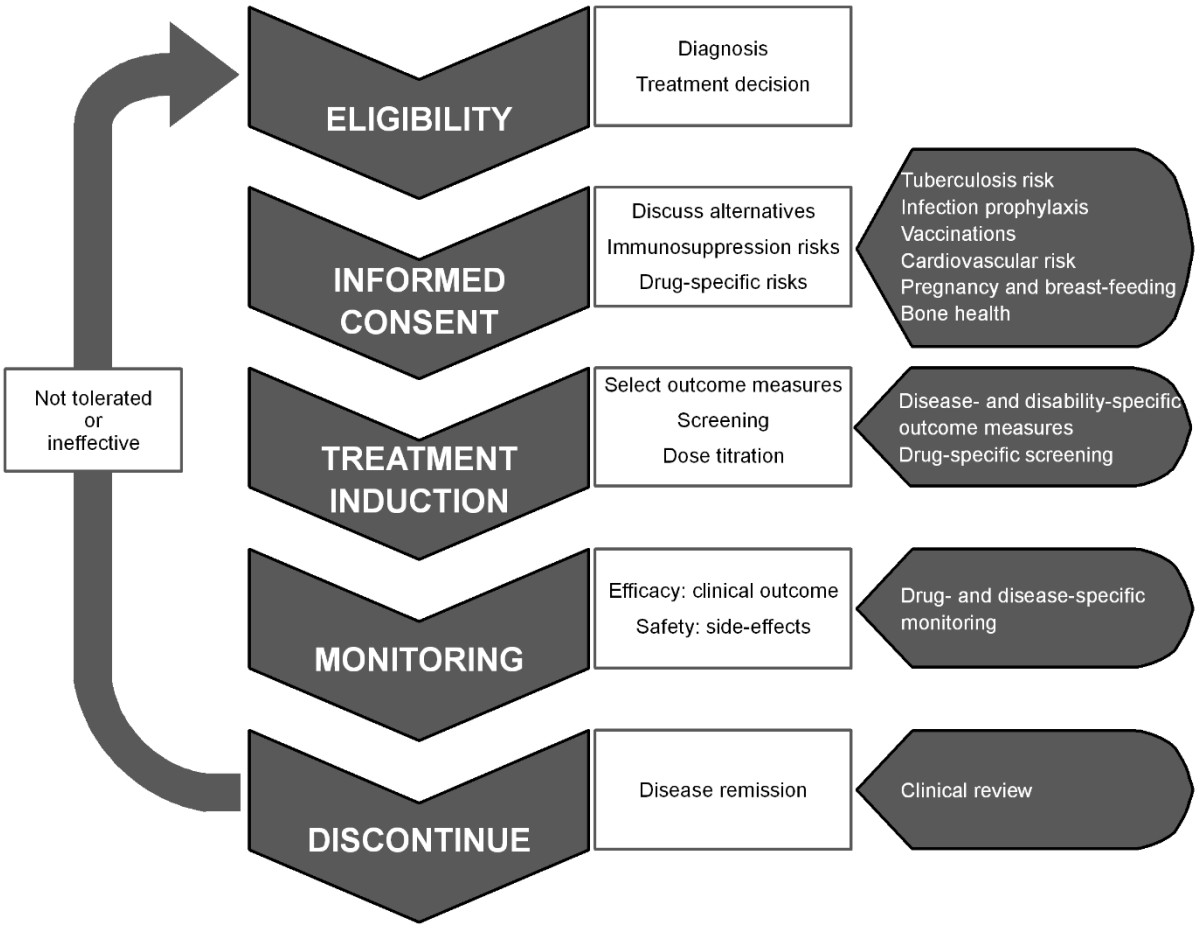

Figure 1: Approach to immunosuppression in neuromuscular diseases

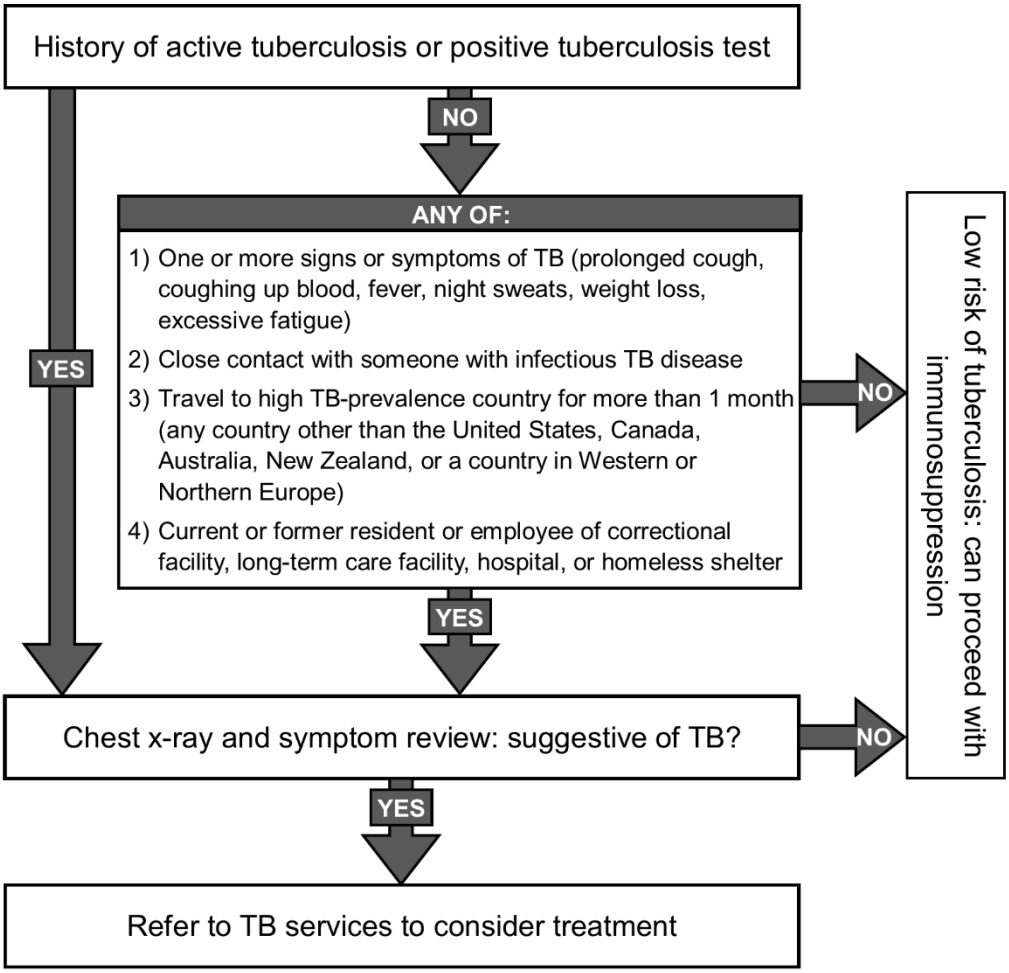

Figure 2: Algorithm for the consideration of tuberculosis (TB) treatment

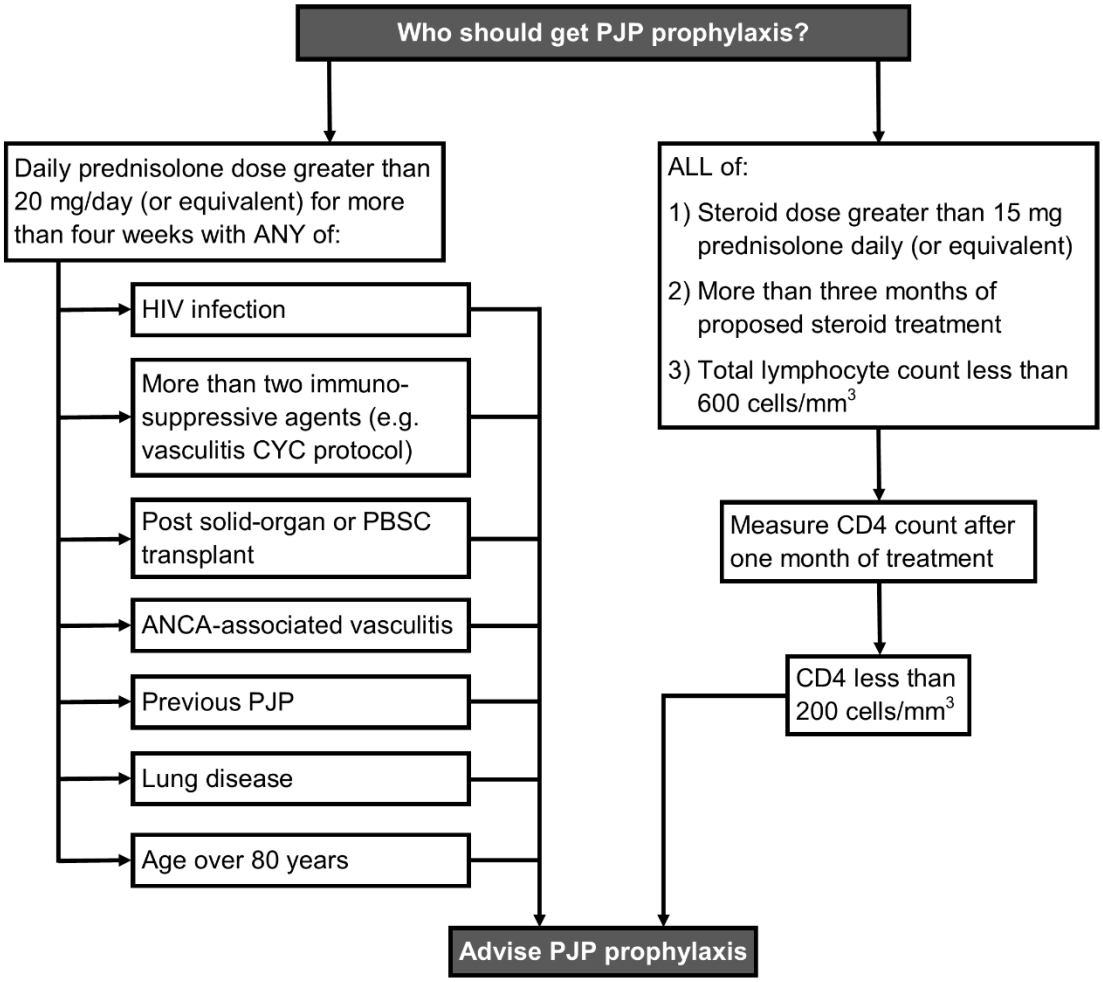

Figure 3: Algorithm for the consideration of *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis; ANCA: anti-neutrophil cytoplasmic antibody; CYC: cyclophosphamide; HIV: human immunodeficiency virus; PBSC: peripheral blood stem cell

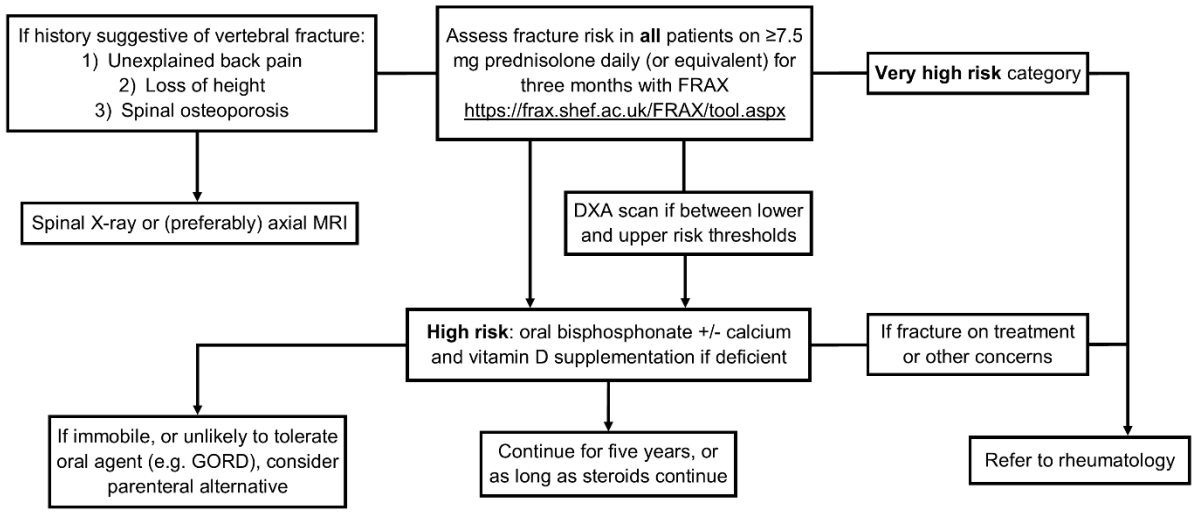

Figure 4: Assessment and treatment of bone health; GORD: gastro-oesophageal reflux disease