Immunosuppression guidelines during COVID-19 outbreak

General Health Advice (from DHSC/PHE/FCO, updated 23 April 2020)

1. The risk of Coronavirus remains high
2. The government published its coronavirus action plan on 3 March. The Prime Minister has issued strong and clear guidance on 23rd March 2020 to **STAY AT HOME**
3. The Health Protection (Coronavirus) Regulations 2020 have been put in place to reduce the risk of further human-to-human transmission in this country by keeping individuals in isolation where public health professionals believe there is a reasonable risk an individual may have the virus.
4. Advice from PHE is updated daily https://www.gov.uk/guidance/coronavirus-covid-19-information-for-the-public

COVID-19 and neurological autoimmune diseases

High dose steroids in acute severe inflammatory conditions

- Avoid high dose steroids in all but life threatening/ sight threatening/ severely disabling and rapidly progressive inflammatory neurological presentations
- When considering high dose steroids discuss with at least one other consultant colleague for consensus decision.
- Patients on >20mg prednisolone equivalent per day are considered at high risk, <10mg per day at low risk. Additional oral immunosuppression may increase risk. See Table 2 here

IVIG

- Immunoglobulin confers no additional risk or benefit to patients with coronavirus at the current time. Patients attending hospital for regular infusions may meet additional risk from public transportation and/or associating with hospital patients in infusion units.
- Patients on IVIG in the UK should have already been optimised to their lowest frequency infusion and lowest dosage according to NHSE guidelines and these should continue (high use, high risk of relapse, severe disease on previous relapse). However, others may fall into one of the following stratified groups:
    i. patients who have not been actively optimised to a maximal interval could be spaced to a greater interval to reduce hospital exposure (relapse risk)
    ii. patients who have only sensory symptoms and no measurable disability could stop. Some patients may wish to stop themselves in this situation
    iii. patients who are on more frequent low dose cycles and fractionated doses for headache management can be returned to baseline frequency with headache management as possible.

It is important that any patients who do relapse can quickly be re-infused if these strategies are taken

Myasthenia Gravis

Early data indicate that chloroquine and hydroxychloroquine and azithromycin (possibly other macrolides) are beneficial in severe COVID infection. These agents have potential to worsen neuromuscular transmission and precipitate MG crisis. These should not be routinely prescribed to patients with MG and used cautiously only in specific circumstances.

Disease-modifying therapies/ Immunosuppression

People who are immunosuppressed *may* be at increased risk of COVID-19 infection based on evidence from previous viral pandemics (Collins et al., 2019) . Publicly available, although not peer-reviewed published data from the ICNARC database report immunocompromise (chemotherapy, radiotherapy or daily high dose steroid treatment in previous 6 months) – (7/196 admissions - 3.7%) as the most frequent serious co-morbidity in COVID19 patients requiring ITU admission in the UK, followed by renal (2.1%), respiratory (1.6%), haematological (1.1%) and other malignancies (1.1%). Age over 60 (70%), male sex (70.9%) and elevated BMI (71.4% BMI>25) also highlighted. To March 20th 33 had and ITU outcome with 48.5% mortality.

Larger studies identified no patients with *immunosuppression* with complications for poor outcomes from coronavirus in Italy, China or previous coronavirus epidemics (D'Antiga L 2020 Liver Transplantation), and neither Guan et al (NEJM 2020) nor Onder et al (JAMA 2020) report any association data. Patients with comorbidities (cardiovascular disease, diabetes, chronic respiratory disease, hypertension, cancers) had higher case fatality rates (10.5%, 7.3%, 6.5%, 6.0%, 5.6% respectively) than those without comorbidities (0.9%) (Wang et al.,2020) as per ICNARC. Thus, although government pragmatic and sensible guidance is to avoid new immunosuppressants and combinations of possible, patients on immunosuppressants for active disease suppression should remain on those.

In essence, neurologists need to balance as far as possible the risks and harms of delaying DMTs with the risks and harms of patients needing DMTs who could acquire COVID-19 in the community. The risks of withdrawal from immunosuppression and precipitating a flare of disease may be greater than the risk of stable low level immunosuppression. The general impression from PHE/DHSC statements is that COVID-19 will rise in the next couple of months and there may be a summer lull. Conventional seasonal coronaviruses tend to be winter viruses. The seasonality of COVID-19 is as yet unknown

	Patients initiating treatment	***Patients already on treatment***
Treatments with low-risk of infections		
IVIg/ SCIg PLEX	General health advice Initiate treatment as usual	General health advice Continue treatment
DMTs/ treatments with risk of infections with a long duration of action		
Ocrelizumab Rituximab Cyclophosphamide	General health advice Consider delaying initiation of treatment or an alternative DMT, taking into account the risks and benefits. Anti-CD20 antibodies may significantly suppress adaptive humoral immunity to novel pathogens	General health advice If treatment due consider checking CD19 count along with routine FBC and immunoglobulin levels. If patient is neutropenic, lymphopaenic and/or CD19 <1% consider delaying treatment course, taking into account the risks and benefits.
Immune-reconstitution therapies		
Cladribine HSCT	General health advice	General health advice

Footnotes

[1] Careful attention should be paid to lymphocyte counts, ensure >0.5x10^9

	Do not initiate treatment, consider an alternative DMT	Delay further courses of treatment, taking into account the risks and benefits, and reassess periodically
Steroid-sparing agents		
Azathioprine[1] Methotrexate Mycophenolate	General health advice Consider delaying initiation of treatment or an alternate DMT, taking into account the risks and benefits	General health advice If clinically stable then continue treatment, taking into account the risks and benefits, and reassess periodically. • NB. Risk of relapse risk/ relapse treatment

Blood monitoring for immunosuppressant medications

The British Society of Rheumatology and the British Society of Gastroenterology have both recommended that monitoring frequency should be reduced to a minimum. Initiation of new drugs will still require standard monitoring. Immunosuppressants in combination should be monitored at usual frequency. Oral immunosuppression monotherapy at stable dose (azathioprine, methotrexate and mycophenolate) can all reasonably be monitored 3-monthly. Monitoring bloods (FBC, LFT, U&E) could reasonably be taken in primary care to reduce exposure to secondary care facilities.

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