Immunosuppression in ILD

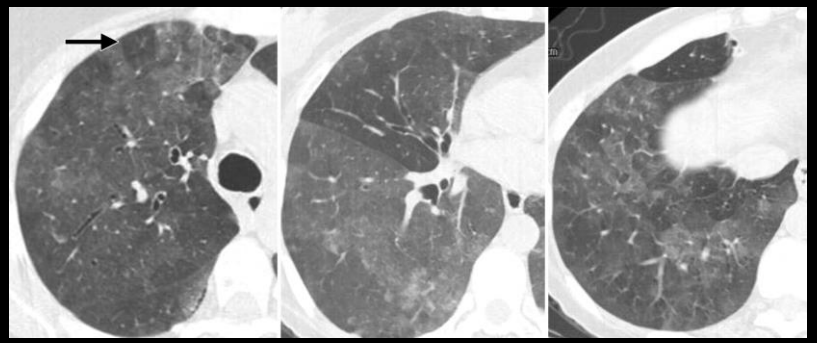
Sarah Mulholland

Immunosuppression?
Immunomodulation?
Immunotherapy?

Informed consent

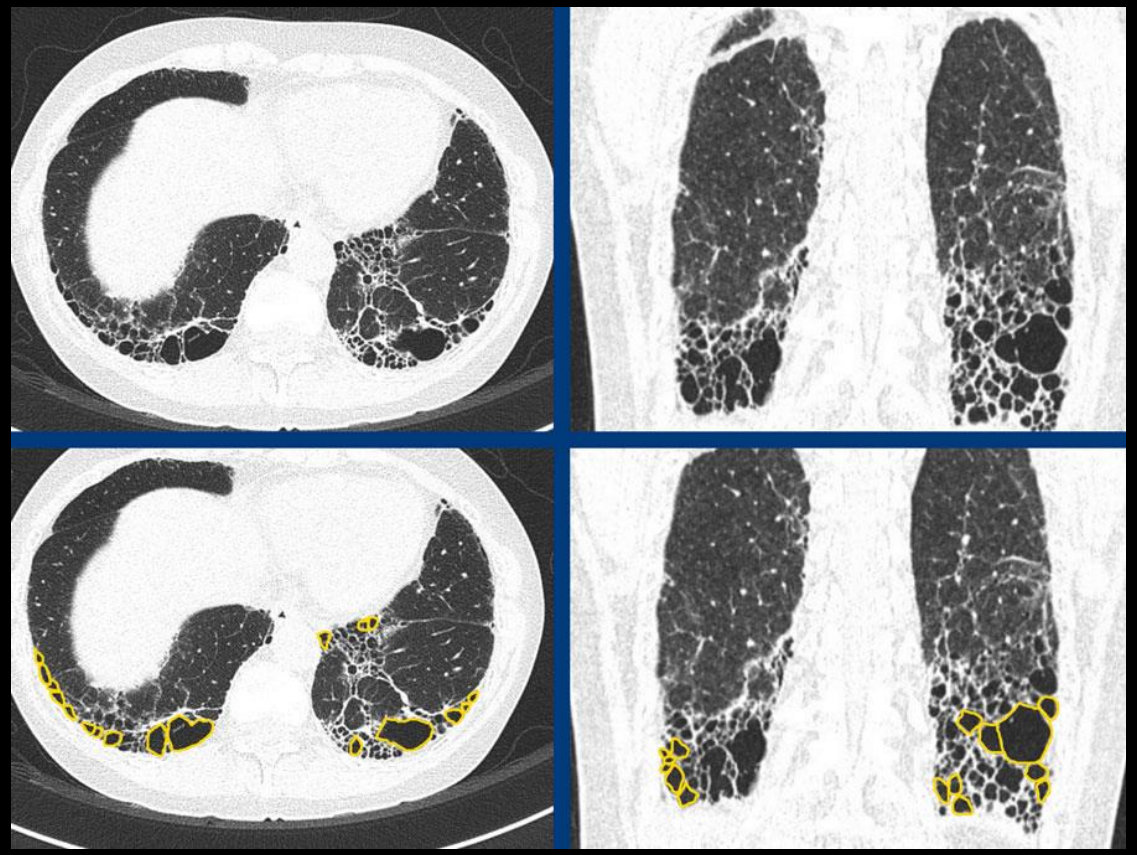
- What are you treating?
- What will happen if I don’t have treatment?
- Will the treatment work?
- How will you measure that it works?
- Is it safe for me to take?
- What are the side effects?
- What should I do if I get any side effects?
- How will you make sure it continues to be safe for me?

What ARE we treating with immunomodulation?



II. Interstitial lung diseases		
a. Disorders associated with increased percentage of specific BAL cell types		
Lymphocytic cellular pattern	Eosinophilic cellular pattern	Neutrophilic cellular pattern
>15% lymphocytes	>1% eosinophils	>3% neutrophils
Sarcoidosis	Eosinophilic pneumonias	Collagen vascular diseases
Nonspecific interstitial pneumonia (NSIP)	Drug-induced pneumonitis	Idiopathic pulmonary fibrosis
Hypersensitivity pneumonitis	Bone marrow transplant	Aspiration pneumonia
Drug-induced pneumonitis	Asthma, bronchitis	Infection: bacterial, fungal
Collagen vascular diseases	Churg-Strauss syndrome	Bronchitis
Radiation pneumonitis	Allergic bronchopulmonary aspergillosis	Asbestosis
Cryptogenic organizing pneumonia (COP)	Bacterial, fungal, helminthic, *Pneumocystis* infection	Acute respiratory distress syndrome (ARDS)
Lymphoproliferative disorders	Hodgkin's disease	Diffuse alveolar damage (DAD)

What AREN'T we treating with immunomodulation?



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prednisone, Azathioprine, and *N*-Acetylcysteine for Pulmonary Fibrosis

N Engl J Med 2012;366:1968-77.

Table 2. Safety End Points.*

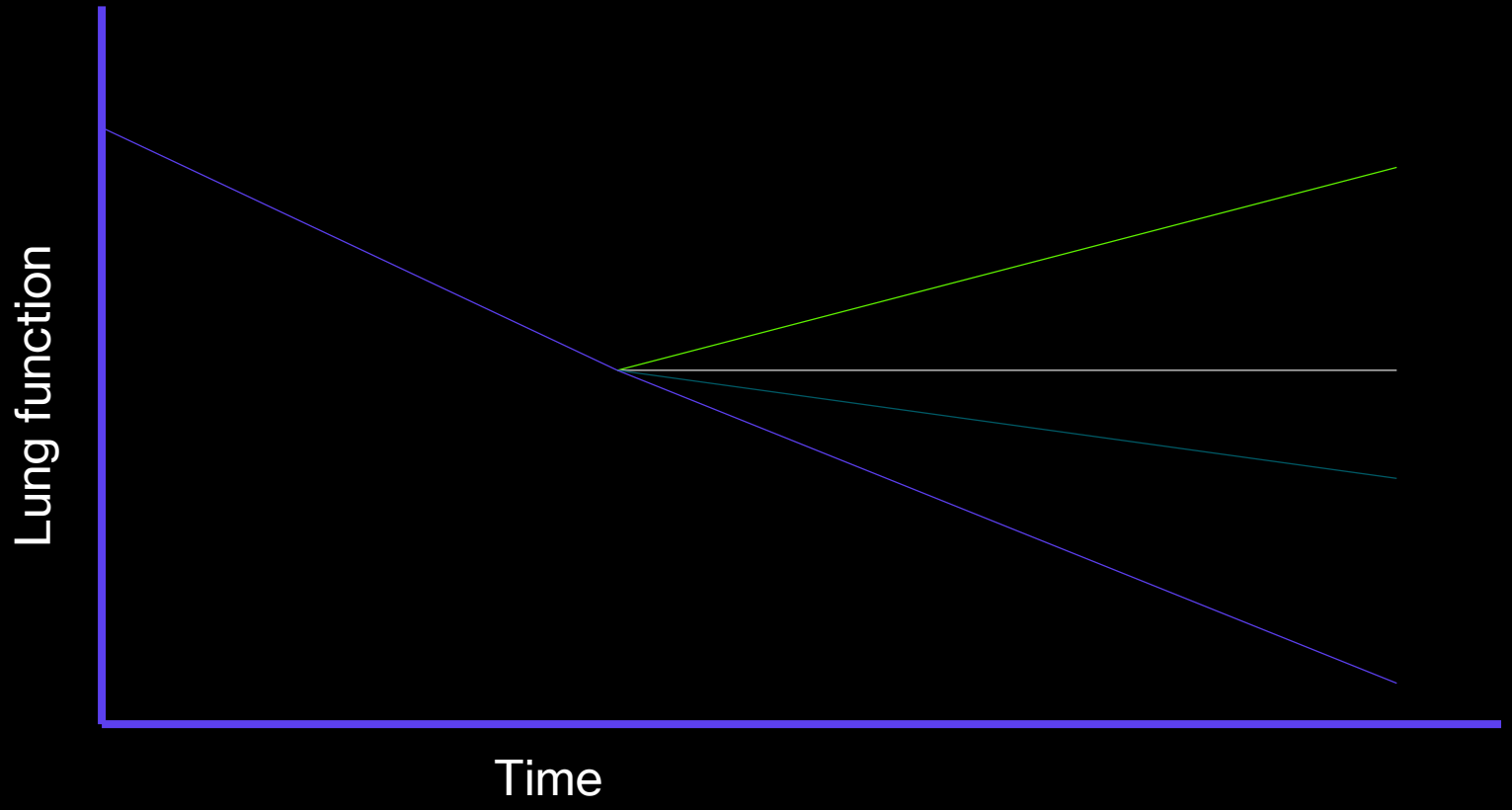
End Point	Combination Therapy (N=77)	Placebo (N=78)	Hazard Ratio	P Value
Death — no. (%)				
From any cause	8 (10)	1 (1)		0.01
From respiratory causes	7 (9)	1 (1)		0.02
Hospitalization for any cause — no. (%)	23 (30)	7 (9)		<0.001
Acute exacerbation — no. (%)	5 (6)	0		0.03
Serious adverse event — no. (%)	24 (31)	8 (10)		0.001
Based on Kaplan–Meier estimate at 60 wk — % (95% CI)				
Death from any cause	19.8 (9.9–37.2)	2.0 (0.3–13.6)	9.26 (1.16–74.1)	0.01
Death from any cause or hospitalization	43.6 (30.7–59.0)	16.9 (8.7–31.5)	3.74 (1.68–8.34)	<0.001
Death from any cause or ≥10% decline in FVC	36.3 (23.7–53.0)	32.4 (19.7–50.3)	1.46 (0.70–3.05)	0.30

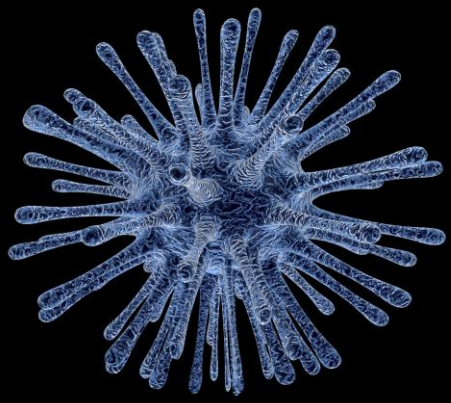
What do we use to treat what?

- No consensus guideline
- Adapted from Van den Bosch et al.

Condition	Treatments	Approach
CTD-ILD, IPAF	Prednisone	First line[30,31,32,41]
	MMF	First line with prednisone or second line[13,40,41,79]
	AZA	First line with prednisone or second line[16]
	RTX	Third line[22,62,63,68]
	CYC	Third line[58,80]
RA-ILD	MTX	Second line if required for joint disease[81,82]
	Tocilizumab	Fourth line[83]
SSc-ILD	MMF	First line[11]
	CYC	Second line[11,52]
	RTX	Third line[20,64]
	Tocilizumab	Third line[84]
Vasculitis or Dermatomyositis with hypoxemic respiratory failure	Methylprednisolone pulse	First line[85]
	CYC	First line[50]
	RTX	Second line[75,86]
	AZA	Third line (maintenance only)[87]
	MMF	Third line (maintenance only)[13,88]
NSIP	Prednisone	First line[89]
	MMF	Second line[79]
	AZA	Second line[89]
	CYC	Third line[19,89]
HP	Prednisone	First line[9,29]
Chronic HP	MMF	Second line[12,43]
	AZA	Second line[12,43,46]
Sarcoidosis	Prednisone	First line[8,89]
	MTX	Second line[15,49]
	AZA	Second line[15]
	RTX	Third line[21]
	Infliximab	Third line[90]
Fibrosing organizing pneumonia	Prednisone	First line[89]
	MMF	Second line[91]
	CYC	Second line[92]
Eosinophilic pneumonia	Prednisone	First line[7]

Why are we using immunosuppression?





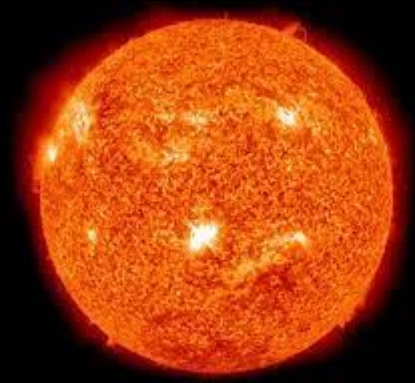
Pre immunosuppression screen

Infections? TB, Hep B, Hep C, HIV, EBV, CMV, VZV

Kidneys

Liver

Calcium and Vitamin D



Do we need PJP prophylaxis?

Pneumocystis jirovecii

The fungus formerly known as PCP

No consensus

Consider in high risk patients:

- Older patients
- Previous infection
- +++ immunosuppression
- Cyclophosphamide
- Rituximab (?)

Co-Trimoxazole 960mg 3 x week or 480mg OD

What about vaccinations?

- Covid
- Flu
- Pneumonia
- Shingles

“Immunocompromised individuals represent the highest priority for vaccination given their risk of severe disease, and therefore the programme aims to catch up all immunocompromised individuals aged 50 years and over in the first year of the programme implementation.”

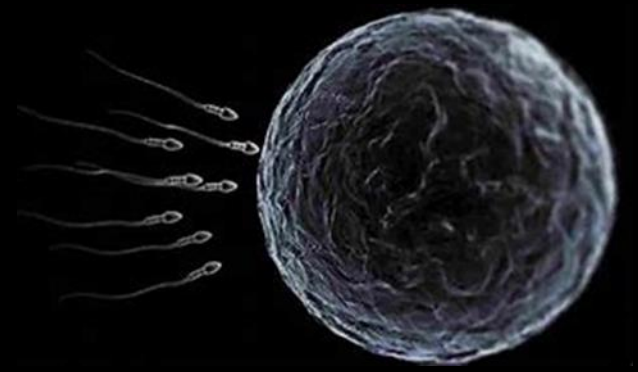
Public Health England | Department of Health

Immunisation against infectious disease

Avoiding infections

- Avoid close contact with people who have an infection
- Practice good hand hygiene and consider carrying a hand gel
- Brush your teeth regularly
- Stop smoking if you're a smoker
- Make sure your food is stored and prepared properly
- Try to keep your house clean and hygienic, especially the kitchen, bathrooms and toilets

Conception and fertility



	Peri-conception	1st trimester	2nd/3rd trimester	Breastfeeding	Paternal exposure
Prednisolone	Y	Y	Y	Y	Y
IV methylprednisolone	Y	Y	Y	Y	Y
Methotrexate (≤25mg/week)	Stop ≥ 1 month prior	N	N	N	Y
Azathioprine	Y	Y	Y	Y	Y
Cyclophosphamide	N	N	N	N	N
Mycophenolate mofetil	Stop ≥ 6 weeks prior	N	N	N	?
Infliximab	Y	Y	Y	Y	Y
Rituximab	May be considered to manage severe maternal disease if no other pregnancy-compatible drugs are suitable. If used in third trimester, avoid live vaccinations in infant vaccination schedule until 6 months of age.			Y	Y

Adapted from: 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 2023;62:e48–88

Where do I get my prescriptions?

Appendix 1: Medicines Suitable for Shared Care

The following medicines have been identified as being suitable for shared care as defined within this policy. Shared care protocols will be developed for the agents listed below.

Medicines not listed below may still be suitable for shared care but have not been identified for national shared care protocol development at the current time.

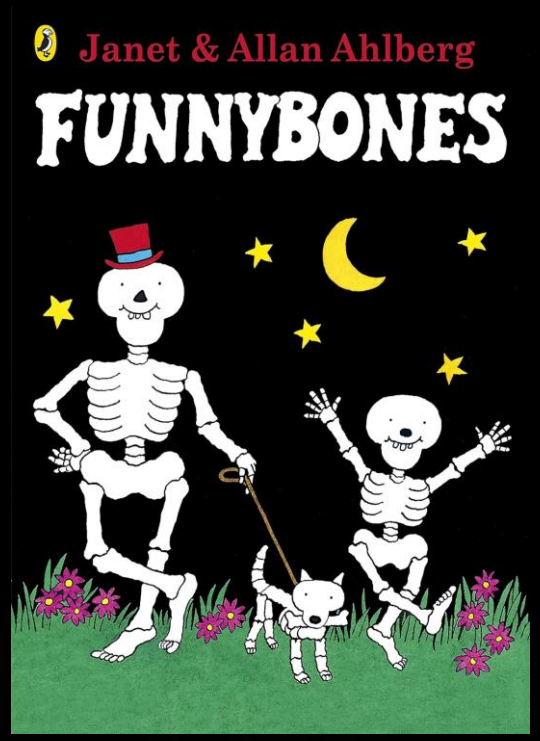
Drug	Specialist initiation recommended	Medicine is suitable for primary care prescribing	Medicine requires regular monitoring, which can be carried out in primary care but may require the advice of a specialist
Amiodarone	✓	✓	✓
Atomoxetine	✓	✓	✓
Azathioprine	✓	✓	✓
Ciclosporin	✓	✓	✓
Dexamfetamine	✓	✓	✓
Dronedarone	✓	✓	✓
Guanfacine	✓	✓	✓
Hydroxycarbamide	✓	✓	✓
Hydroxychloroquine	✓	✓	✓
Leflunomide	✓	✓	✓
Lithium	✓	✓	✓
Lisdexamfetamine	✓	✓	✓
Mercaptopurine	✓	✓	✓
Methotrexate	✓	✓	✓
Methylphenidate	✓	✓	✓
Mycophenolate	✓	✓	✓
Riluzole	✓	✓	✓
Sulfasalazine	✓	✓	✓

- Variable agreements
- National shared care
- Check your formulary for local shared care
- Who does the monitoring?

Corticosteroids

- Prednisolone 30mg PO OD and wean
- Methylprednisolone 1g IV for 3 consecutive days
- Inhibit gene expression of cytokines decreasing T cell proliferation
- Reduce b cell antibody synthesis
- Physiological cortisol ~ 7.5mg prednisolone
- May need short synacthen test prior to stopping

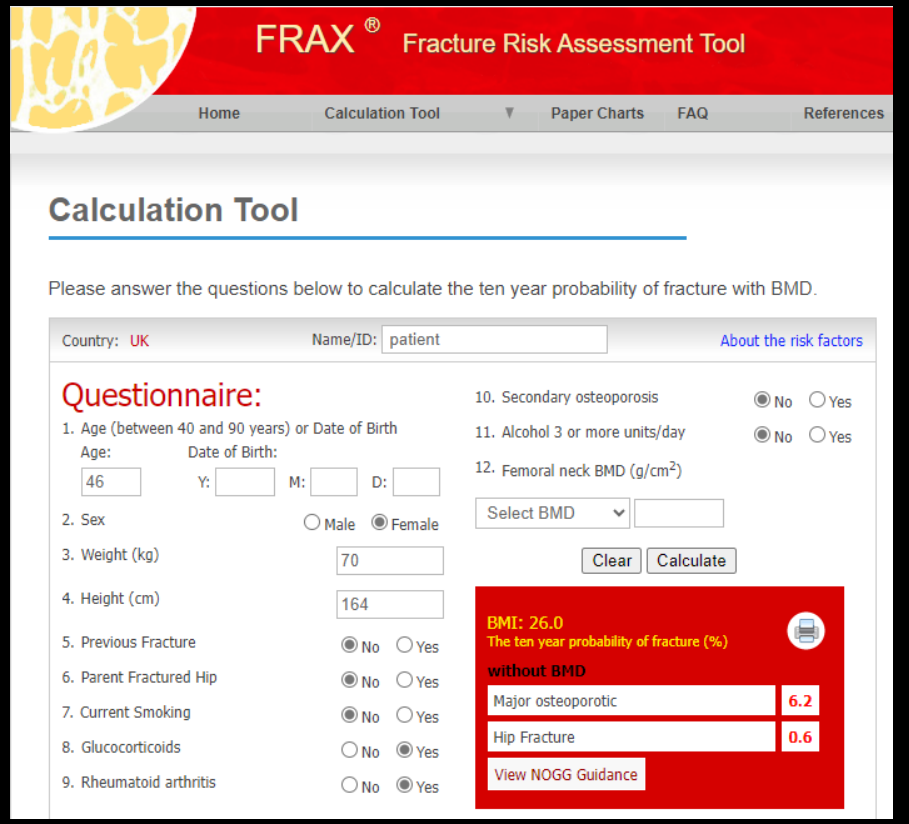
Corticosteroids



Bone health

Assess if pred ≥ 7.5mg OD ≥ 3 months

- Calcium
- Vitamin D
- Bisphosphonate



Corticosteroids

Steroid Emergency Card (Adult)

NHS

IMPORTANT MEDICAL INFORMATION FOR HEALTHCARE STAFF

THIS PATIENT IS PHYSICALLY DEPENDENT ON DAILY STEROID THERAPY as a critical medicine. It must be given/taken as prescribed and never omitted or discontinued. Missed doses, illness or surgery can cause adrenal crisis requiring emergency treatment.

Patients not on daily steroid therapy or with a history of steroid usage may also require emergency treatment.

Name.....

Date of Birth ..... NHS Number .....

Why steroid prescribed .....

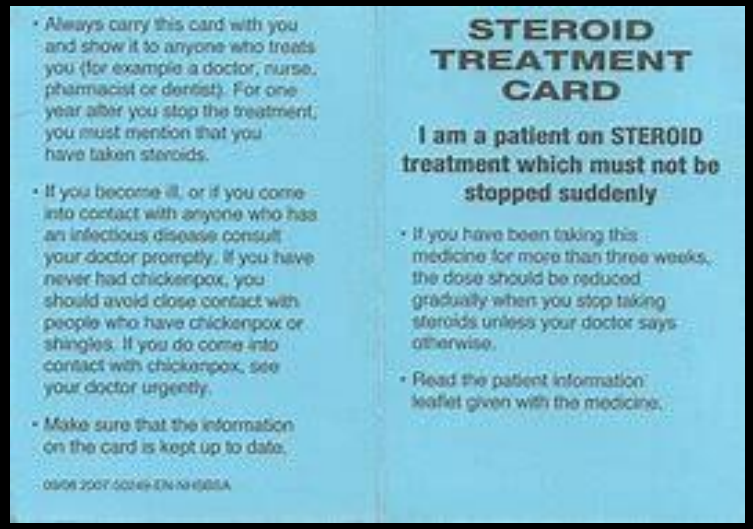
Emergency Contact .....

When calling 999 or 111, emphasise this is a likely adrenal insufficiency/Addison's/Addisonian crisis or emergency AND describe symptoms (vomiting, diarrhoea, dehydration, injury/shock).

Emergency treatment of adrenal crisis

1) **Immediate** 100mg Hydrocortisone i.v. or i.m. injection. **Followed by** 24 hr continuous i.v. infusion of 200mg Hydrocortisone in Glucose 5% **OR** 50mg Hydrocortisone i.v. or i.m. qds (100mg if severely obese).
2) Rapid rehydration with Sodium Chloride 0.9%.
3) Liaise with endocrinology team.

Scan here for further information or search https://www.endocrinology.org/adrenal-crisis



- Always carry this card with you and show it to anyone who treats you (for example a doctor, nurse, pharmacist or dentist). For one year after you stop the treatment, you must mention that you have taken steroids.
- If you become ill, or if you come into contact with anyone who has an infectious disease consult your doctor promptly. If you have never had chickenpox, you should avoid close contact with people who have chickenpox or shingles. If you do come into contact with chickenpox, see your doctor urgently.
- Make sure that the information on the card is kept up to date.

STEROID TREATMENT CARD

I am a patient on STEROID treatment which must not be stopped suddenly

- If you have been taking this medicine for more than three weeks, the dose should be reduced gradually when you stop taking steroids unless your doctor says otherwise.
- Read the patient information leaflet given with the medicine.

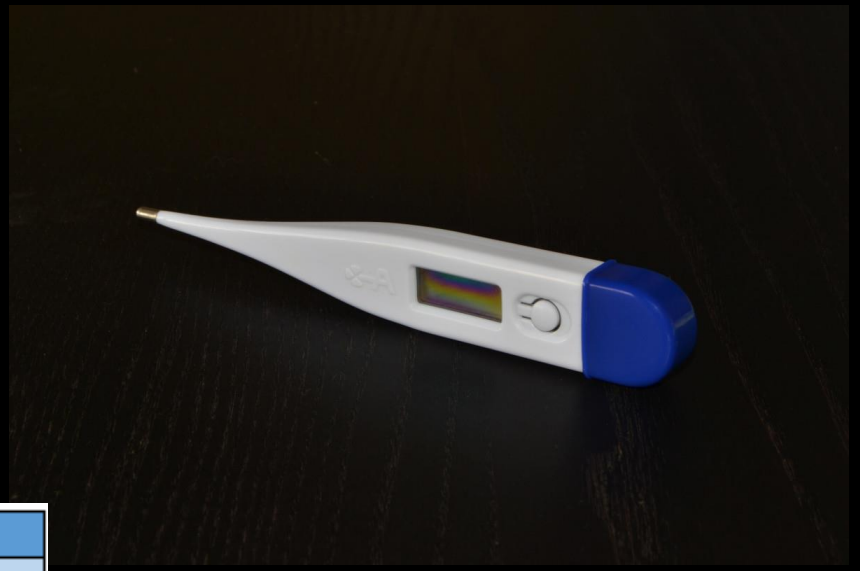
Prednisolone 5mg or more for greater than 4 weeks

Multiple short courses of oral steroids (≥3 in 12 months)

All oral steroids for>3 weeks

Less than 3 weeks or multiple courses discretionary

Sick day rules



Sick Day Rules - Steroid Adjustment			
Steroid medication	**Normal Dose**	**Unwell with fever**	**COVID - suspected or confirmed**
Prednisolone	3-10mg daily	5mg twice daily	10mg twice daily
Prednisolone	10 mg or more daily	Split daily dose to twice daily	Split daily dose to twice daily, e.g. 20mg daily - take 10mg twice daily
Hydrocortisone	>10mg daily	20mg immediately, then 10mg 6 hourly	20mg every 6 hours
Other steroid preparation	N/A	20mg hydrocortisone immediately, then 10mg 6 hourly	Hydrocortisone 20mg every 6 hours

General counselling

Common in first 24-72h - Feeling sick, upset stomach and diarrhoea

May happen in weeks months - Mouth ulcers and thinning of hair

Stop treatment immediately and seek urgent medical advice if:

- Chest pain or shortness of breath (with or without a dry cough) - lungs
- New or severe itching of the skin with or without yellowing of the whites of the eyes or long term dark urine - liver
- Bleeding gums, Tarry stools, new or unexplained bleeding or bruising – bone marrow suppression
- Severe and continuing diarrhoea or vomiting (due to risk of dehydration)
- Severe or blistering, skin rash, ulceration or soreness of the skin

Avoid direct sunlight, wear high protection sunscreen and cover up

Alcohol intake must be kept within normal recognised limits due to the potential risk of severe liver damage.

Blood monitoring

Initial monitoring and at dose change: To be repeated every 2 weeks until the dose has been stable for 6 weeks, then monthly for 3 months:

· FBC

· U&Es, including creatinine and CrCl

· LFTs, including AST and/or ALT, and albumin

Following a dose increase repeat every 2 weeks until the dose has been stable for 6 weeks, then revert to previous schedule.

More frequent monitoring is appropriate in patients at higher risk of toxicity.

Methotrexate

NHS
National Patient Safety Agency

Methotrexate treatment

• Oral methotrexate pre-treatment patient information leaflet

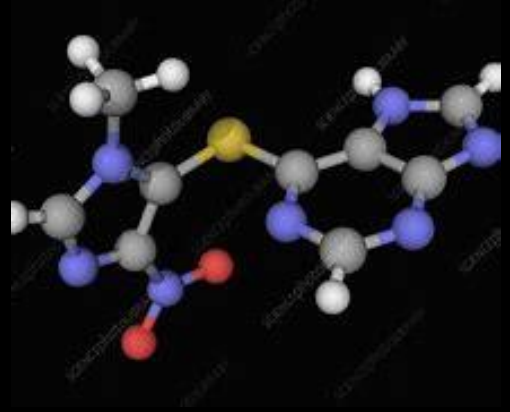
This leaflet has been prepared to support information given to you as part of your discussions with the doctor, nurse or pharmacist before you start treatment with oral methotrexate. This leaflet should be used to help you in these discussions. The specialists you are seeing may also provide you with some information about your condition and how to take your methotrexate.

Every bottle or carton of medicine you collect from your pharmacy will also contain important information that you should read.

This leaflet does not cover information for children or young people with arthritis treated with methotrexate. For information on treatments for children refer to: **www.bspar.org.uk**

- Folate analogue
- Titrate up to 15-20 mg/week – CHECK STRENGTH
- Folic acid 5mg once a week (at least)
- Cautioned/Contraindicated in renal impairment
- Monitoring
- Side effects
  - + Gastrointestinal
  - + Fatigue, malaise, headache
  - + Mouth ulcers

Azathioprine



- Inhibits purine synthesis and DNA replication in lymphocytes
- Thiopurine methyl transferase levels
- 1-3 mg/kg
- 50% dose if intermediate TPMT
- 25% dose if taking allopurinol
- Monitoring

Side effects

- Gastrointestinal
- Fatigue, malaise, headache

Specific side effects

- Acute pancreatitis
- Malignancy

https://www.gloshospitals.nhs.uk/our-services/services-we-offer/pathology/tests-and-investigations/tpmt/

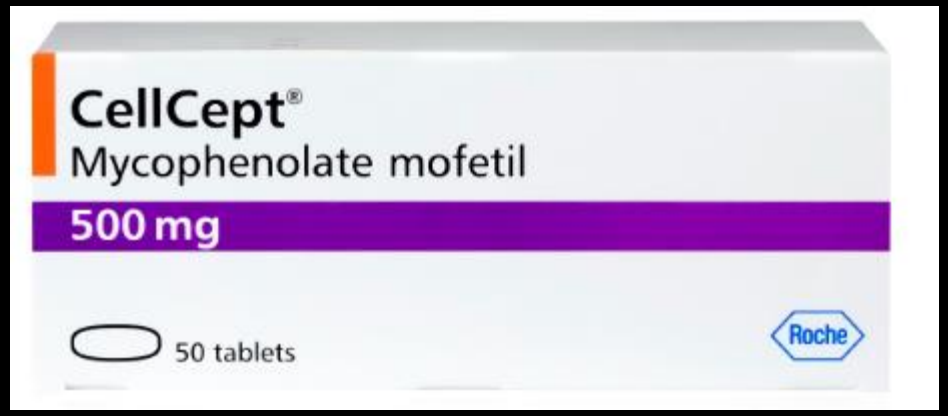
Whole blood TPMT activity	Reference range (nmol/h/g Hb)
Deficient	<10
Carrier	10 - 25
Normal	26 - 50
Raised	>50

Mycophenolate

- Inhibits inosine monophosphate dehydrogenase and purine synthesis
- Up to 3g/day in 2 divided doses
- Monitoring

Side effects

- Gastrointestinal
- Fatigue, malaise, headache
- Malignancy



Cyclophosphamide

- Alkylating immunosuppressant
- Inhibits b lymphocyte activity and antibody synthesis

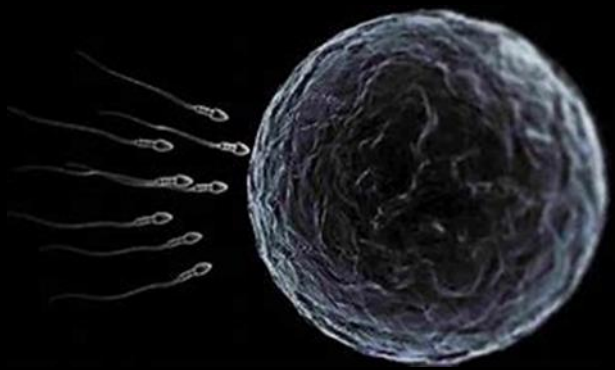
- Scleroderma - RECITAL 600mg/m^2 BSA 4 weekly for 6 doses
- Vasculitis - CYCLOPS 15mg/kg 3 Infusions at 2 weekly intervals then 7 infusions at 3 weekly intervals
- Total lifetime maximum dose is 20g

- Monitoring at Baseline and ≤ 48h before each subsequent infusion:
  FBC, U&Es (including renal function), LFTs, CRP and urine dip

Dose modification of pulsed Cyclophosphamide as used in CYCLOPS trial - www.vasculitis.org/protocols/CYCLOPS			< CYLOPS regimen often used as basis for dose adjustments for age and renal function If used consider capping at 1.2 grams cyclophosphamide Consider basing dose on ideal body weight in obese patients (BMI >30)
Age (years)	Creatinine		
	<300 micromol/L	300-500 micromol/L	
< 60	15 mg/kg ☐	12.5 mg/kg ☐	
60 – 70	12.5 mg/kg ☐	10 mg/kg ☐	
> 70	10 mg/kg ☐	7.5 mg/kg ☐	

Cyclophosphamide

- Feeling or being sick – ondansetron pre infusion + ondansetron and domperidone PO to go home
- Fertility – consider cryopreservation
- Can cause bladder irritation – keep well hydrated (and co-prescribe mesna PO 400mg -2h, +2h and +6h)
- Can cause metallic taste in the mouth/nasal stuffiness during infusion
- Malignancy



Rituximab

- Anti CD20 monoclonal antibody reducing pathogenic antibody production
- 1000 mg at weeks 0 and 2 intravenously up to 6 monthly
- Monitoring at Baseline and ≤ 48h before each subsequent infusion:
  + FBC, U&Es (including renal function), LFTs, CRP

Specific side effects

- Reactivation of Hep B (discuss with gastro re prophylaxis)
- Risk of hypogammaglobulinaemia with repeated courses
- Neutropenia (can occur long after infusion, check FBC if signs of infection)
- Progressive multifocal leucoencephalopathy

Infliximab

- anti-tumour necrosis factor-α (Anti-TNF) antibody
- 3-7.5mg/kg week 0, 2 and 6 and then 8 weekly
- Monitoring at Baseline and ≤ 48h before each subsequent dose:
  + FBC, U&Es (including renal function), LFTs, CRP

Specific side effects

- Reactivation of Hep B (discuss with gastro re prophylaxis)
- Malignancy – ?lymphoma, sun safety in view of melanoma risk
- central nervous system demyelinating disorders
- Interstitial lung disease

Randomized Controlled Trial > Lancet Respir Med. 2021 Jan;9(1):96-106.
doi: 10.1016/S2213-2600(20)30330-1.

Efficacy and safety of nintedanib in patients with systemic sclerosis-associated interstitial lung disease treated with mycophenolate: a subgroup analysis of the SENSCIS trial

Kristin B Highland [1], Oliver Distler [2], Masataka Kuwana [3], Yannick Allanore [4], Shervin Assassi [5], Arata Azuma [6], Arnaud Bourdin [7], Christopher P Denton [8], Jörg H W Distler [9], Anna Maria Hoffmann-Vold [10], Dinesh Khanna [11], Maureen D Mayes [5], Ganesh Raghu [12], Madelon C Vonk [13], Martina Gahlemann [14], Emmanuelle Clerisme-Beaty [15], Mannaig Girard [16], Susanne Stowasser [15], Donald Zoz [17], Toby M Maher [18]; SENSCIS trial investigators

What about antifibrotics?

- The evidence so far suggests safe to continue immunosuppression and immunomodulation
- Monitor
- Consider polypharmacy and side effect profile

	Group 1	Group 2	Group 3	
	IPF	PF-ILD with concurrent immunosuppression	PF-ILD without immunosuppression	Significance*
Total patients	42	44	26	
Nintedanib dose reduction (n, %)	14 (33.3)	8 (18.2)	11 (42.3)	p=0.08
Nintedanib discontinuation (n, %)	12 (28.6)	12 (29.5)	8 (30.8)	p=0.981

Summary

- Collaborate with colleagues in other specialities
- Appropriate counselling and consent – patient should be a partner in their care
- Careful selection of patient and treatment
- Use the lowest effective dose for the shortest time possible
- Monitor for safety and effectiveness of medication


THANK YOU FOR LISTENING
ANY QUESTIONS?

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