University of East Anglia

PHA 6020Y

Person centered medicine from bench to bedside

Rheumatoid Arthritis Workshop

Learning Outcomes
Answers

- Critique the prescribing of medication for the treatment of Rheumatoid Arthritis in line with NICE NG 100 and EULAR 2022 RA guidance.
- Identify signs and symptoms used in the diagnosis of RA.
- Identify considerations required when starting therapy in RA patients.
- Clinically assess prescriptions to identify actual/potential prescribing and pharmaceutical care issues for patients with RA.
- Provide appropriate solutions to identified issues.
- Identify monitoring parameters pharmacists must review to maintain the safety and ensure efficacy for patients on medication for the treatment of RA.
- Determine important counselling points for patients newly started on medication for RA.

Case Study 1

Flatplace GP Surgery Medical Notes (BT, MRS)

Patient Details

Surname:	T	Sex:	Female
Forename 1:	B	D.o.B:	18/01/1976
Forename 2:		Age:	47 y
Address:	7 Roman Road	Ethnicity:	White caucasian
	Flatplace	NHS#:	558 998 8898
	FL28 9QE	Usual GP:	Dr Hannah Goodman
		Pharmacy:	Flatplace Pharmacy

Clinical Records

Active Problems: Hypertension – diagnosed December 2016.

Past Medical History: Nil relevant

Current Repeat Medication: Amlodipine 10mg OD, Ramipril 10mg OD, Atorvastatin 20mg OD

Acute Medication: Nil relevant

Drug allergies & sensitivities: Penicillin

Family History: Mother – angina, Father – Died from MI age 68, sister – type 1 diabetes.

Current Weight: 64kg
Current Height: 165 cm

Social history: Occupation - personal assistant,
Diet - Good diet (fruit, veg and home cooked foods),
Exercise - walks dog regularly,
Alcohol - limited alcohol (special occasions),
Smoking - 7-15 cigarettes daily (for past 19 years).
Caffeine – 2 cups of tea / day

Clinic/Test Results

Date	BP
Sept 2023	130/70
Sept 2022	135/75
Jan 2022	140/80
Nov 2021	150/80
Sept 2021	158/85
Sept 2020	136/73

Consultation notes

14/08/23 10.20 Dr Sarah Parry

Patient describes fatigue, weight loss and fever over the previous 8-12 weeks. Upon further investigation, she also reported intermittent polyarticular stiffness and swelling of the first and second metacarpophalangeal joints on both hands which was most severe upon waking.

OE: Positive metacarpophalangeal squeeze test, difficulty forming and releasing a fist, swelling, warm to touch and tender area.
BP: 132/76

Referral to Rheumatologist – Flatplace hospital.

09/10/23 08.30 Dr Sarah Parry
Letter received from Flatplace hospital.

Diagnosis – Rheumatoid arthritis

1. **Which symptoms described for Mrs BT contribute to the diagnosis of RA?**

Non-specific symptoms – fatigue, weight loss and fever.

Intermittent polyarticular stiffness and swelling of the first and second metacarpophalangeal joint. Symptoms most severe on waking (duration 30 mins to several hours usually reflects severity of joint inflammation)

'Suspected persistent synovitis of undetermined cause' – NICE NG100

Positive squeeze test
Difficulty forming and opening a fist

Swelling, warm to touch and tender areas.

2. **In addition to the symptoms reported by the patient and the signs on physical examination, what additional tests would contribute to a diagnosis of RA?**

Acute phase response – CRP, ESR
Rheumatoid factor (anti-CCP if Rheumatoid factor negative)
X-ray

These (or some of them) may be done by the GP before the patient is seen by the rheumatologist. Anything not already done during diagnosis should be done afterwards to form a baseline for comparison in the future.
The functional ability of the patient should also be assessed with i.e. Health Assessment Questionnaire (HAQ).

3. **Based on the NICE NG 100, what is the recommended course of treatment for Mrs BT?**

Offer first line treatment with conventional disease-modifying anti-rheumatic drug (cDMARD) **MONOTHERAPY** using oral METHOTREXATE or LEFLUNOMIDE or SULFASALAZINE as soon as possible. (Hydroxychloroquine is a weak DMARD and can be used if mild symptoms/palindromic disease, although it is not as effective).

'Treat-to-target' aim for remission DAS <2.6.

Escalate dose as tolerated, aim for escalation to effective doses in 4 -6 weeks.

Consider short term bridging treatment with a corticosteroid. This will provide immediate reduction in joint inflammation and pain relief as the DMARD has a lag time until effects are seen. Steroids may not be required by all it depends on each individual patient.
Corticosteroid use should be reviewed at every visit with the aim to remove it once cDMARD is active (generally by 3 months). Patients should not remain on corticosteroids due to the ADR risks.

Under EULAR the initial treatment is – 'Methotrexate as part of the first treatment strategy'. This means methotrexate should be tried first; by using the term 'strategy' it could mean it is used as mono or combined therapy, although monotherapy was considered in the recommendation to be most appropriate due to the reduced risk of side effects.

4. **What drug factors should be considered when deciding on the initial treatment for Mrs BT? (You should consider the precautions, cautions/contraindications, side effects, dosing and monitoring)**

   ****Please complete for directed study following the workshop****

Patient preference / clinician preference.

There are currently no robust RCT's demonstrating differences in efficacy with these three agents. Therefore, choices are made based on patient characteristics (i.e. co-morbidities) and drug characteristics, see below:

Cautions / contraindications
MTX:
Active infection – because MTX can cause immunosuppressive effect and therefore reduce the efficacy of the immune system to fight infection.
Ascities / pleural effusion – MTX is distributed into the fluid, accumulates and can be re-excreted to prolong serum half-life increasing the risk of toxicity.
Immunodeficiency syndromes – it causes an immunosuppressive effect.
Significant hepatic impairment/liver disease – increased with concomitant hepatotoxic drugs.
Alcoholism (increased risk of hepatotoxicity from MTX).
Severe renal impairment – MTX is renally cleared therefore impairment would lead to accumulation and increased risk of S/E – ensure adequate hydration. Dose should be reduced in renal impairment. Care required with NSAIDs (use under supervision of the rheumatologist and not OTC) due to the risk to renal function and MTX excretion.
Blood dyscrasias - Myelosuppression is a side effect therefore may worsen this.

Pregnancy – MTX is teratogenic. Contraception required in males and females during treatment and for 3-6 months afterwards.
Elderly – caution due to reduced folate reserves and reduced renal and hepatic function.
Consider interactions - antifolate agents. Folate deficiency increases MTX toxicity.

Sulfasalazine:
Hypersensitivity to parent molecule (sulfasalazine), 5-aminosalicylic acid or sulfapyridine (sulphonamide abx or salicylates).
Impaired hepatic or renal function – responsible for metabolism and excretion.
Blood dyscrasias – it can inhibit absorption and metabolism of folic acid and can cause deficiency potentially resulting in blood disorders.
Asthma – see below.
Glucose-6-Phosphate Dehydrogenase deficiency – it can increase the risk of haemolytic anaemia.

Leflunomide:
Hypersensitivity
Liver impairment – the active metabolite is cleared by hepatic metabolism and biliary secretion, therefore impairment will increase the risk of accumulation.
Hypoproteinaemia – highly protein bound therefore plasma levels expected to be higher if protein low.
Immunodeficiency
Bone marrow impairment
Serious infection
Moderate/severe renal impairment
Pregnancy – women of childbearing potential should use effective contraception during treatment and for up to 2 years after (if washout procedure not carried out).
Possible male mediated foetal toxicity, therefore effective contraception required during treatment and should undergo the washout procedure prior to conception.

Side effects
MTX:
Generally, the frequency and severity is dependent on dose and duration. If adverse events occur, it is sometimes possible to hold treatment/ alter the dose and restart cautiously.
Folinic acid can sometimes be used to improve/correct toxic effect. Concomitant folic acid can be used to reduce S/E.
Common S/E – malaise, fatigue, chills, fever, dizziness, leucopenia, infection, N&V&D, alopecia.
Hepatotoxicity (MTX is hepatotoxic) – changes may occur without prior signs of toxicity - monitor.
Myelosuppression – MTX can suppress haematopoiesis. This can occur abruptly - monitor.
Respiratory effects (stop treatment and do not re-start). Patients should be aware of the signs to be aware of (dry cough, dyspnoea, thoracic pain) and HCP should monitor at each visit. They can occur acutely during any stage of therapy.
GI side effects – Diarrhoea and ulcerative stomatitis (toxic effects, requiring interruption of treatment). Therefore, caution in those with peptic ulcer or ulcerative colitis. General non-serious GI S/E often require dose reduction.
Skin reactions – these can be serious and should be reported immediately.
Patient to be able to identify and report signs of these S/E to allow appropriate investigations.

Sulfasalazine:
Common S/E: nausea, headache, rash, loss of appetite, raised temperature, insomnia, tinnitus.
Blood disorders – leucopenia > thrombocytopenia and neutropenia. Generally reversible on cessation.
Cough, dyspnoea (therefore it is cautioned in patients with reduced pulmonary reserve, i.e. asthma).
Nausea – very common. Abdominal pain, diarrhoea, vomiting, stomatitis.

Pruritus.
Arthralgia.
Proteinuria (also crystalluria and other renal effects). Need to ensure adequate fluid intake.

Leflunomide:
Common S/E: mild increased BP, mild allergic reactions, diarrhoea, N&V, abdominal pain, elevation of liver enzymes (may require dose adjustment), paraesthesia, headache, dizziness, increased hair loss, rash, itching dry skin.
Colitis – therefore need to investigate diarrhoea
Severe liver injury – if it is to occur it most commonly in the first 6 months (especially when co-treatment with other hepatotoxic drugs).
Blood disorders – mild leucopenia > anaemia and mild thrombocytopenia. Increased risk when given with other haematotoxic drugs.

Special precautions
MTX:
Dehydration, impaired renal function and co-administration with medicines that may cause renal impairment (i.e. NSAIDs – close monitoring required) – due to these increasing the risk of MTX levels.
Alcohol use, hepatotoxic drugs (including hepatotoxic DMARDs i.e. leflunamide, close monitoring required if used together) – increase the risk of hepatotoxicity.
Concomitant use of haematotoxic drugs – myelosuppression is common, occurring without warning within the normal dosing range. Additional drugs increase the risk of this occurring.
Patient should report any signs of infection.
Avoid additional antifolate drugs such as trimethoprim as these increase the risk of bone marrow suppression.
Use with folic acid once a week (increased to every day except methotrexate day) to reduce side effects.
Can be given by SC or IM if GI side effects intolerable (increased expense).

Sulfasalazine:
Safest for use in pregnancy (give with folic acid as folic acid absorption is inhibited).
Enteric coated version licensed in RA. Do not crush or take with antacids.
NSAIDs can be taken.
Sulfasalazine may colour urine orange/yellow and stain contact lenses orange.
Can cause oligospermia and infertility in men – effects reversed in 2-3 months of stopping treatment.
Slow acetylator status – it is taken up and acetylated in the in the liver. This acetylated version of sulfapyridine is renally excreted, therefore slow acetylators can have accumulation of the drug.
Due to the similarity on structure, sulphonamide have caused hypoglycaemia – monitor.
Myelosuppression, haemolysis or hepatoxicity have occurred – patients should report signs of bleeding, bruising, sore throat, fever, jaundice and malaise.

Leflunomide:
Concurrent hepatotoxic/haematotoxic drugs – increased risk of serious S/E.
Active metabolite (A771726) has a long half-life (1-4 weeks) meaning adverse reactions may occur even if treatment has stopped. If this needs to be removed from the body rapidly then the washout procedure should be followed.
Active metabolite of leflunamide is highly protein bound and cleared via hepatic and biliary metabolism – levels therefore expected to be higher in those with hypoproteinaemia or impaired liver function.
Patients with impaired bone marrow function or low cell red/white cell counts are at increased risk of haematological disorders.

Due to its immunosuppressive effect it may increase susceptibility to infections.

Monitoring

MTX:

FBC, LFT, renal function checked before initiations and weekly until stabilised. Then every 2-3 months. – This is because MTX can cause bone marrow suppression, pulmonary toxicity are potential risks of treatment/SE. A chest x-ray should be done prior to initiation – due to the risk of pulmonary effects.
MTX is renally cleared and therefore checked as impairment would increase the risk of S/E.
Patient self-reporting signs of hepatic, pulmonary and blood disorders.
MTX book given to patient.

Sulfasalazine:

FBC and LFT before treatment, every other week (during the first three months of treatment) for 3 months, monthly for 3 months then every 3 months.
Renal function when beginning therapy (at initiation and monthly for the first 3 months).

Leflunomide:

LFT and FBC at initiation and every 2 weeks during the first 6 months and every 8 weeks thereafter.

Dosing

MTX:

2.5mg-5mg (some references say up to 10mg) administered a week prior to initiation of therapy to detect any idiosyncratic adverse reactions.
Weekly (7.5mg to 20mg ONCE a WEEK – the dose is usually increased by 2.5mg to 5mg every 2-6 weeks)
Effect seen in 6 weeks to 3 months
Dose can be adjusted based on side effects and response.
Day should be the same each week and specified on the prescription.
Only 2.5mg tablets should be used and multiples of these taken to make up the required dose.

Sulfasalazine:

Gradual increase in dose (1 tablet daily, increased by 1 tablet a day each week until on 1 QDS or 2 TDS – as tolerated) – this improved GI S/E.
Slow to effect, 6-8weeks to 3 months.

Leflunomide:

Loading dose can lead to more S/E. Without loading dose it has a longer time to effect.
100mg OD for 3 days then maintenance 10-20mg.
Therapeutic effect starts 4-6 and may further improve up to 4-6 months.

For all:
Live vaccines should not be used with any DMARD.
Patients should be up to date with their immunisation before initiation and should receive the influenza and pneumococcal vaccine each year.
Caution use of all three preparations in patients with inactive chronic infections where immune response is important or essential, i.e. TB and hepatitis B & C.

The consultant decides to start her on methotrexate; you receive her prescription in the hospital pharmacy:

Methotrexate 10mg tablets
20mg once a WEEK
Supply: 28
Folic acid 5mg tablets
5mg weekly
Supply 4 tablets

5. Would you want to discuss this prescription with the prescriber before dispensing it? If so, what would you want to discuss and why?

Yes.

Strength of tablets it is available as 2.5mg, 10mg (10mg NOT used due to an NPSA safety alert). It is always important to check the dose with the patient and ensure they are taking them correctly. (There have been occasions where a patient has received a different strength but known they always take 'four' – so received 40mg instead of 10mg.)

Is 20mg an appropriate starting dose? BNF, Moderate/severe: 7.5mg WEEKLY adjusted according to response, max 20mg weekly. Start with 7.5mg weekly increase by 2.5mg -5mg to 20mg (maximum dose) or highest dose tolerated below the max.

May consider a test dose (2.5mg) initially to determine any idiosyncratic adverse reactions.

Is it appropriate to supply 28 tablets? Generally, you would only supply up to the next appointment to reduce the risk of taking them incorrectly (if dispensing from a larger pot). Otherwise, if in specially labelled original plaster packs, these should be dispensed complete to enable all of the information to be given to the patient.

Should folic acid be prescribed with MTX? Generally, only once a week (to begin with) on a different day to the MTX. This is given to reduce the incidence of antifolate side effects that are experienced with MTX.

Bridging course of corticosteroids - Due to the delay to DMARD effect (of up to 3 months). Prescribing depends on the patient (not everyone will have it). This may be in the form of an oral prednisolone course or one-off IM or IV methylprednisolone or intraarticular inj. These should only be used for a relatively short period of up to 3 months and stopped appropriately.

Day of the week for administration should be stated (information added to the label, mtx booklet checked).

MTX booklet.

6. In groups of 3, allocate a pharmacist, Mrs BT (the patient) and an observer.
   Undertake a patient consultation for the new initiation of methotrexate. Use your pre-workshop task material to support your knowledge and enable you to play any of the roles.

   During feedback, you will be expected to share your counselling points and sequence of discussion.

Role play the patient
Explain that you have been struggling to type and use a pen due to the swelling in your joints, you are anxious that you will have to give up your job

The doctor did give you some paracetamol and codeine – can you take these with the MTX?

What is it for?
- Reduces over activity of the immune system, works by suppressing this over activity of the immune system. NOT pain relief.

Dosage administration: once WEEKLY dose, day of administration M – Monday for Methotrexate, (although it can take ANYDAY!!).

What to do if you miss a dose – take it the following day. Do not take the dose if you are three or more days late (a flare up is unlikely in this time). In both cases take your dose on the normal day on the following week.

How long will it take to work? 6 weeks to 3 months. Use of the corticosteroid will provide you more immediate relief to reduce pain and swelling until the MTX is fully effective. The corticosteroid will then be stopped – this is not a long-term therapy.

MTX is a cytotoxic drug (toxic to living cells) – therefore handle with care, keep out of reach of children, if female – appropriate contraceptive is necessary as it's teratogenic.

You will be given a booklet to record your blood test results, and any changes in dose. Carry this with you and ensure your doctors fill it in. Needs to be up to date. Show to any HCP you need to see.

You will need regular blood tests to monitor your therapy/adverse effects, this will reduce your risk of some adverse effects as intervention can be made prior to them occurring.

As with all medicines there can be side effects for example:
Side effects:
GI – nausea, diarrhoea (these normally settle-inform prescriber if they persist) and stomatitis (inflammation of mouth and lips) – need to inform prescriber so they can investigate whether this is a S/E or toxic effect requiring intervention.

CNS – headache, drowsiness and blurred vision – inform prescriber.
Hair thinning – generally returns to normal upon stopping.

Advise patients to report any signs of infection – including sore throat – as they may be signs of immunosuppression.
Yellowing of the whites of the eyes, N&V – as they may be signs of hepatic impairment.
SOB, dry cough, fever – as they may be signs of pulmonary toxicity.

By informing the prescriber about observed effects, they can investigate the cause and make appropriate interventions to ensure safety and disease control. Dose alterations of MTX and folic acid may be required.

Cautions - You would want to investigate the following to see if they would impact on your patient:
Alcohol in moderate, increased risk of liver impairment
Do not have contact with anyone with chicken pox (seek advice if you do), avoid any live vaccinations whilst on methotrexate
Avoid self-medicating with Ibuprofen OTC and possible drug interactions with other medicines.

Avoid non-pasteurised foods.

Appropriate contraceptives are required during treatment and for 3-6 months afterwards.

Inform practitioners of the MTX – would stop prior to surgery, interacts with medicines and can decrease ability to fight infection.

7. What tests and investigations should be done before and during methotrexate therapy?

LFT's, RF, FBC Chest X ray

Newly started patients: FBC and LFT's/RF before starting therapy and every 1-2 weeks until stabilised there after every 2-3 months. Local policies may vary.

FBC to check for - neutropenia, thrombocytopenia and lymphopenia, bone marrow suppression. This can occur abruptly or over time.

RF to ensure MTX can be cleared and does not accumulate.

LFT to ensure no underlying impairment as MTX is hepatotoxic.

Chest X ray: pulmonary toxicity

Patient symptoms, ESR, CRP – to check for efficacy.

After regular drug monitoring and dose escalation to methotrexate 20mg weekly, Mrs BT's DAS28 was recorded as 2.1, (8 months after starting therapy).

After a stable couple of years, Mrs BT contacted her specialist nurse with a flare in her symptoms and is seen as a priority by the rheumatologist. She has increased stiffness on waking (lasting greater than 30 minutes and after resting, increased pain and swelling of her hands and with new symptoms in her ankles. She is also feeling generally unwell and tired. She reports difficulty with her everyday tasks such as brushing her teeth and typing at work. She is quite down and upset that her symptoms are worse again.

Her recent blood results were as follows:

CRP	**40mg/L**	(<10mg/L)
WBC	**20.4**	(4-11x10^9/L
RBC	4.9	(4.6-6.5x10^{12}/L)
Hb	**88**	(115-164g/L)
Platelets	222	(150-400x10^9/L)
Neutrophils	7.2	(2-7.50x10^9/L)
Lymphocytes	1.5	1.10-3.50x10^9/L)
ESR	**65**	(1-15mm/h)
Bilirubin	14	(0-22µmol/L)
Albumin	40	(35-50g/L)
Alkaline Phosphate	84	(38-126U/L)
ALT	40	(0-50U/L)
GGT	50	(0-60U/L)

Creatinine	95	(55-125mmol/L)
Sodium	138	(134-145mmol/L)
Potassium	4.0	(3.6-5.0mmol/L)
Urea	6.0	(1.7-7.1mmol/L)

8. According to NICE NG 100, what is the next step in the treatment recommendation for Mrs BT?

As the MTX has already been optimised, the next step in therapy needs to be considered.

'Step-up strategy'.

Offer additional cDMARD (MTX, SSZ, LEF) in combination when the treatment target has not been reached. NICE does not specify which agent should be used. So, Mrs BT would receive MTX plus another cDMARD.

(Potentially consider bridging corticosteroids – ensure they are stopped appropriately).

Potentially - symptomatic pain relief – i.e. NSAID with caution and close monitoring.

Optimise the new therapy.

Increased monitoring until stabilised.

9. According to NICE NG100, what is the next step in the treatment recommendation for Mrs BT if the patients target is not reached?

Biologic or tDMARDS as discussed in the NICE TA, used for either moderate or severe disease, i.e. anti-TNF agents, anti-IL-6 (sarilumab/tocilizumab), antibody blocking t-cell activation (co-stimulation modulator) (abatacept), anti-b-cell antibody (rituximab), or 'nibs(considering the drug characteristics/risks of each).

You would make the prescribing decision based on patient and drug characteristics, if there was no clear agent indicated the most cost effective should be chosen.

Can be used with MTX as no contraindication to this.

Consider bridging corticosteroids.
Symptomatic pain relief.

Optimise the new therapy.

Case Study 2

Mr TW is a 35 year old man who has been taking sulfasalazine and methotrexate combination therapy for the past 6 months after optimised methotrexate monotherapy failed to induce remission. On review he continues to have active symptoms of RA: pain and swelling in both knees and 5 joints of each hand, tenderness in 4 joints of each hand and morning stiffness of about 2 hours. He has detectable RF and ACPA. His DAS28 calculated to be 5.2 on review by the rheumatologist.

He has also been taking diclofenac 50mg tablets TDS and paracetamol 1g tablets QDS.

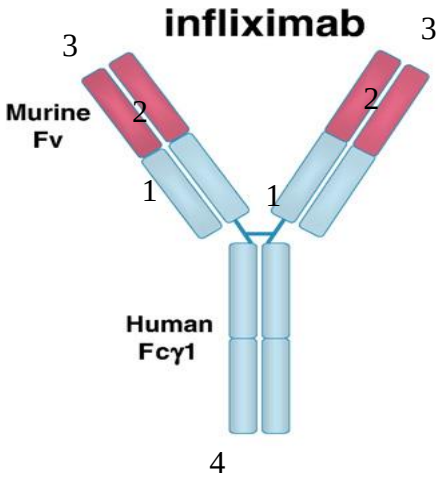
1. Mr TW is prescribed infliximab 300mg IV with MTX (sulfasalazine stopped). Based on the NICE NG 100 and EULAR 2022, comment on the appropriateness of this.

NICE NG 100 refers you to technology appraisals for the use of bDMARDs. TA 375 refers to anti-TNF agents in severe disease. It has also relatively recently (2021) been considered appropriate for moderate disease (DAS 3.2-5.1).

After failure of optimised combined cDMARD therapy, in severe disease (i.e. DAS28 >5.1) biological DMARD therapy should be considered. ***Mr TW fits this criteria***. (In practice, you are likely to see other anti-TNF agents given that can be administered outside the hospital setting (i.e. home) by the patient/carer).

EULAR comments upon this. Mr TW has poor prognostic factors – active disease after cDMARD treatment and after combination treatment, presence of RF and ACPA and a high DAS28. According to EULAR the guidance is to add in a bDMARD or tDMARD-(only after risk has been assessed).

2. What is the mechanism of action of infliximab? Consider how you would explain the mechanism of action to a patient?



Monoclonal antibody made of IgG light (1) and heavy chains (2).
Two FAB (Fragment of antigen binding) – TNF binding areas (3).
Linked to a Fc region (4) – this part dictates the antibodies capabilities, i.e. complement fixation and Fc receptor binding.

Infliximab is a tumour necrosis factor alpha (TNFα) inhibitor) and binds with high affinity to monomers and trimers of soluble TNF and transmembrane TNF and can form complexes of each. This prevents pro-inflammatory TNF from binding to either one of its receptors reducing its effect) and can also induce other outcomes that reduce TNFs effect on inflammation. Outcomes include reduced cytokine and chemokine production, reduced activation and proliferation, inflammatory cell apoptosis, reduced angiogenesis and reduced effects on bone.

It is a chimeric protein made of human and murine origin.

Explanation to patient:
Infliximab is a manufactured "antibody". Antibodies are normally produced by the body to fight against harmful bacteria. Tumour necrosis factor alpha or TNFα is a cytokine. Cytokines are substances released by the body during inflammation. Inflammation is a normal process generated by the body to fight against harmful bacteria and viruses. Normally, this inflammation is controlled and regulated. In rheumatoid arthritis this process breaks down, therefore the joints of patients with rheumatoid arthritis become inflamed, excessive production of TNFα can lead to inflammation and damage to joints. but infliximab has been designed to bind to TNFa and reduce it's effect on causing inflammation.

3. What are the administration instructions for infliximab?

Check that the patient has been weighed as the dose is 3mg/kg and the dose is based on 100kg.
Doses given at 1, 2, 6 weeks and then every 8 weeks.
Ensure that it is diluted to 250mL with 0.9% NaCl
Give over a 2-hour period minimum and give slower if signs of reaction (or to reduce the risk of a reaction) – patients to be observed for 1-2 hour post infusion to monitor for acute infusion-related reactions (pre-treatment can reduce the risk of this).

4. What clinical checks would you want to do before supplying the infliximab?

Check that the patient has had pre-treatment testing for TB / heptatitis B / has no active infection / does not have HF / does not have a history or current malignancy or demyelinating disease or is due any surgery (due to further increased risk of infection).

Check that the patient has been prescribed paracetamol, antihistamines and potentially methylprednisolone prior to administration to reduce the risk of infusion reactions.

Check whether the patient is to be continued on methotrexate therapy as infliximab should be used in combination with methotrexate – this can reduce the production of antibodies against the infliximab and the likelihood of infusion reactions.

Check the patients was up to date with their vaccines. Ensure they were not due to have any live vaccines.

Manufacturer recommends adequate contraceptives during and for 6 months after therapy.

The patient had been appropriately counselled, to include:
Drug used to control the disease progression of RA. It will control the inflammation and therefore control the pain and effects of the disease.

Dosing – every 2 weeks for 6 weeks then every 8 weeks. Dose may be altered according to response and blood test monitoring.

Methotrexate to continue as prescribed.

Infusion reactions – anaphylaxis and delayed hypersensitivity possible. Due to this a pre-treatment of antihistamine, hydrocortisone and paracetamol may be given.

Monitoring for infection – you will be closely monitored for infections. Treatment will not be given if you have a serious infection. Treatment can put you at risk of some serious opportunistic infections.

Monitoring for hepatobiliary events – LFT checks and signs/symptoms due to effects on the liver.

Vaccinations – Patient should be up to date when treatment is initiated.

Development of malignancy or lymphoproliferative disorders is a risk of treatment.

Patients should report signs of blood dyscraisias (fever, bruising, bleeding).

Undesirable effects – Viral infection, bacterial infection, neutropenia, leucopenia, anaemia, headache, nausea, tachycardia, flushing, depression, conjunctivitis, skin disorders.

Monitor disease for moderate improvement in RA, denoted by equal/greater than 1.2 to continue therapy.

Additional information from infliximab SPC

Rheumatoid arthritis

3 mg/kg given as an intravenous infusion followed by additional 3 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.

Remicade must be given concomitantly with methotrexate.

Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. Dose adjustments may occur if response is not adequate.

Antibodies to infliximab may develop and have been associated with an increased frequency of infusion reactions. A low proportion of the infusion reactions was serious allergic reactions. An association between development of antibodies to infliximab and reduced duration of response has also been observed. Concomitant administration of immunomodulators has been associated with lower incidence of antibodies to infliximab and a reduction in the frequency of infusion reactions. The effect of concomitant immunomodulator therapy was more profound in episodically-treated patients than in patients given maintenance therapy. Patients who discontinue immunosuppressants prior to or during Remicade treatment are at greater risk of developing these antibodies.

5. What monitoring requirements are necessary while the patient has the infliximab infusion?

Anaphylactic reactions can occur within seconds or within a few hours the infusion, therefore recommended that the patient is observed for 1-2 hours post administration.

If acute infusion reactions occur then stop the infusion, emergency treatment should be available such as adrenaline, antihistamines, corticosteroids and breathing apparatus.

Monitor for symptoms of delayed hypersensitivity if re-administered after a prolonged period.

A month later Mr TW is admitted to hospital and diagnosed with a severe community acquired pneumonia. He is started on Co-amoxiclav IV and Clairthromycin IV. You review him on the ward.

6. Would you advise that they continue or stop Mr TW's RA treatment? Please provide the rationale for your decision.

We do not know how long this is after starting treatment with infliximab or how well controlled his RA is now. In either situation there is the need to review the infliximab and MTX in light of the serious infection (serious defined as requiring hospitalisation or IV abx). Both therapies can cause myelosuppression and reduce the effectiveness of the body to manage/clear infection. Continued use may mean the infection cannot be treated, may spread, become more severe and may be fatal.

It is important that the rheumatologist is involved.

You would want both the MTX and infliximab held until the abx treatment cleared the infection (or until IV to PO step down could occur / patient could be discharged, i.e. outside acute stage of infection, when, in severe RA cases they would cautiously restart treatment with close monitoring).

Consider symptom control as RA treatments on hold.