Medicines in Rheumatoid Arthritis
ABOUT US

The National Rheumatoid Arthritis Society (NRAS) is the only patient-led charity in the UK focusing specifically on rheumatoid arthritis (RA), and Juvenile Idiopathic Arthritis (JIA), and providing information, support, advocacy and campaigning for people living with RA and JIA, their families, carers and health professionals involved in their treatment and care.

ASK US

Our freephone helpline 0800 298 7650 is open from 9.30am to 4.30pm, Monday to Friday. Our trained helpline staff, supported by a team of medical and healthcare professionals, are there to answer your questions on all aspects of living with RA.

If you’d like to talk to someone else with RA, the helpline staff can match you with one of our trained telephone support Volunteers, who will then call you back to discuss whatever aspect of living with RA most concerns you. To be put in touch with a Volunteer who has RA, please call the helpline and they will organise a mutually convenient time for the volunteer to call you.

Our website www.nras.org.uk has a wealth of information about all aspects of living with RA, treatments, the latest research and developments, as well as full details of other useful organisations and charities.

The website also links you to an NRAS online forum, NRAS HealthUnlocked, a safe space where you can get peer support and blog about your experiences.

If you don’t have access to the internet or prefer any helpful information sent in the post just call us on 0845 458 3969 or email enquiries@nras.org.uk.

MEET US

Local NRAS groups meet regularly around the country. To find out if there is a group near you visit www.nras.org.uk/groups or email volunteers@nras.org.uk or call 0845 458 3969.

JOIN US

To find out how to support the work of the charity by becoming a NRAS Member see inside the back cover. YOU can make a real difference and help many others living with RA for as little as £20 per year.

CREDITS AND ACKNOWLEDGEMENTS

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REFERENCES

For a full list of all the references (such as to articles in medical journals) used in compiling this booklet, please call NRAS on 01628 823524.
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Foreword

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It is with huge pleasure that I am writing this brief foreword for the National Rheumatoid Arthritis Society (NRAS) medication booklet for RA. As I write, NRAS has recently celebrated its 15th anniversary since its foundation by its inspirational Chief Executive, Ailsa Bosworth MBE. NRAS has worked tirelessly to provide materials that support the lives of those people who develop rheumatoid arthritis and juvenile idiopathic arthritis and importantly, to support and help their loved ones, carers, friends and colleagues.

Over the 15 years since NRAS came into being, and certainly over the last generation, there has been a revolution in our understanding of the biological mechanisms underlying rheumatic diseases, their causes and available drug treatments. All this is very good news indeed as the outlook for someone presenting with new onset rheumatoid arthritis today is better than ever before. Despite developing this condition, which remains incurable at the present time, it is possible for most people to live a full and high quality life. This was not so in past generations.

It is also vitally important for rheumatologists and doctors who see patients with these conditions to be mindful that while the good physician treats the disease, the great physician treats the patient who has the disease! Holistic and compassionate management of inflammatory arthritis, where the team and patient work together to achieve the best solutions for the unique circumstance of every individual, is the ideal approach to optimising quality of life for people living with inflammatory arthritis. And the work that NRAS has contributed to patient support programmes, education, encouragement and friendships, not to mention patient advocacy, and lobbying government to ensure equitable access to specialist services, has been both inspirational and practical in facilitating the best quality of life for people with inflammatory arthritis.

Whether you are someone with an arthritic condition, a healthcare professional, or someone who knows an individual with rheumatoid arthritis, I am sure that you will find this booklet a most useful resource and will join me in thanking NRAS for providing so many resources that support people with RA and enrich their quality of life.
The aims of this booklet

NRAS is delighted to provide the rheumatoid arthritis (RA) community with this resource, the first comprehensive booklet on the range of medications currently available to control the condition. Our aim is to make things as easy as possible for people living with RA to know about the available medications used in their treatment, help them feel more confident about what the future holds and understand why their treatment may need to change from time to time.

The reasons for a comprehensive publication are:

- To provide a short résumé of RA; what it is, why and how it is treated
- To increase understanding that the aim of treatment is to control RA by either achieving remission or sustained low disease activity
- To provide suitable and accessible information for all RA medicines in one booklet
- To outline the possible treatment options available and any likely progressions from one treatment to another
- To increase understanding that any one person will quite possibly have more than one medication, either at the same time or in sequence
- To reassure people coping with RA that during a lifetime some treatments may not work, or work only for a limited period, and other options will be considered
- To explain the four distinct categories of medications, what makes them different from each other and how they fit into the overall picture for the treatment plan
• To give some insight into the possibilities of different treatments in the future

• To outline the guidance of the National Institute for Health and Care Excellence (NICE) and the Scottish Medicines Consortium (SMC) as they relate to these medications for RA

The medicines described in this booklet are available to treat the symptoms felt by people coping with rheumatoid arthritis as well as the biological processes that are known to be responsible. The medical (clinical) management is based on the scientific and proven evidence for improvement and control of the disease.

This booklet does not attempt to give the complete array of the important and vital aspects of help and support, information, physical assessment and treatments that together constitute the whole range of services for treating rheumatoid arthritis.

Information, support and help is available by contacting our Helpline service on 0800 298 7650, on our website www.nras.org.uk and from our many other publications and information sheets. Three further new publications will be launched in 2017: ‘New2RA’ for newly diagnosed patients, ‘Living Better with RA’ for people with existing disease and a booklet on fatigue. In these new booklets other aspects of living with RA like lifestyle, available non-medicine based support and therapies will be covered.
Treating RA

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Rheumatoid arthritis (RA) is a complicated disease that can affect not only the joints but, potentially, other parts of the body as well. It is an autoimmune disease. The body has a complex immune system comprising cells and proteins that work to keep you healthy, by fighting off infections and protecting against cancer. The ‘auto’ of autoimmune disease implies that the immune system has made a mistake and is attacking its own body. In RA this is seen with inflammation (pain and swelling) appearing within the joints. However, as well as this, the whole body may be involved, with a common symptom of extreme tiredness or fatigue, and when the disease is particularly active, feeling generally unwell, with symptoms a bit like flu. Sometimes (although less commonly today due to better treatment) inflammation can develop in places other than joints, such as the eyes, skin or lungs, also people with RA are at greater risk of cardiovascular disease (similar to people with Type II Diabetes).

Research has shown that not all rheumatoid arthritis is the same and it is therefore not ‘one’ disease – there are sub-types. These sub-types are categorised by a blood test called rheumatoid factor (RF) which will be...
either positive (called sero-positive RF) or negative (called sero-negative RF) and this result will influence the choice of treatment. This test is not perfect and false positive or negative results complicate the story requiring the expertise of rheumatologists to make a firm diagnosis.

The blood test for anti-CCP (Cyclic Citrullinated Peptide) inflammatory antibodies has been available for some years, adding to the diagnostic picture. Recent encouraging developments suggest that anti-CCP levels are likely to be a good guide to the future management of RA.

What are the principal aims of treatment?

- To reduce inflammation and its side effects: pain, swelling, stiffness and fatigue
- To protect the body from the risk of damage to the joints and bones caused by uncontrolled inflammation
- To protect other organs in the body that might be affected by uncontrolled inflammation
- To maintain the ability to lead a normal life, with minimal impact on relationships, family, home, work and leisure

When all these aims of treatment are achieved, RA can be said to be well controlled and the individual may be considered to be in remission, or in a low disease activity state. If all these aims are not being achieved, the clinician should adopt a treatment plan referred to as ‘tight control’ – P.14.

Current approach to treatment based on research and long-term evidence

Over the years the treatment for rheumatoid arthritis has changed significantly due to rigorous research into all aspects of the effects of the disease. Also the long term evidence increases each year. Consultants now aim for remission of the disease as soon as possible and to maintain that remission. Someone with RA is considered to be in remission when they have no symptoms of the disease and a Disease Activity Score (DAS) of less than 2.6 (for more information about DAS, P.13).

However, as not everyone with RA has exactly the same disease, doctors do not start all patients in exactly the same way on the same drug regimen. Dependent on the symptoms, the length of time someone may have had the disease prior to diagnosis, the test results and the consultant’s diagnosis, the treatment may include painkillers, a non-steroidal anti-inflammatory drug (NSAID), a single disease modifying anti-rheumatic drug (DMARD) or a combination of DMARDs. Usually, steroids will be added in either as tablets or as an intramuscular (meaning ‘into the muscle’) injection to help treat symptoms whilst the DMARD/s take effect, which can be up to 12 weeks. Regular follow-up visits to the specialist are really important in the early months to enable the clinical team to adjust or alter the treatment to benefit each individual patient. (For more information, see What is the Treat To Target Procedure? P.13.)
The ‘Gold Standard’ for treatment is methotrexate. This can be prescribed as a weekly dose in tablet form or a weekly dose as a small injection just under the skin (subcutaneous). The injection may be started from the beginning of treatment or substituted if the tablets are causing side effects such as nausea.

In an online survey by NRAS in 2015, 645 people with RA responded to the question about whether they were given the choice of weekly tablets or injections at the start of their treatment with methotrexate. The results showed that only 7% were given this choice at the first consultation and only 2% actually started their treatment with injections.

As the whole body may be affected, it makes sense that the most effective treatments are given as tablets or injections that work throughout the body. In the last 20 years there have been massive changes in the treatments for RA (see Development of effective medication for RA, P.51). Medicines that have been used for a long time are now frequently used in combinations and there are many pioneering new drugs (biologic and biosimilar therapies as well as JAK inhibitors) that can control the inflammation within the joints and also switch off the inflammation in the blood.

The NICE Guideline (turn to P.18 for more on NICE guidelines) for the treatment of adults with RA recommends ‘combination’ therapy when you are diagnosed and start on treatment. Combination therapy means treatment with two or more disease modifying anti-rheumatic drugs (DMARDs).

Methotrexate, the ‘gold standard’ DMARD, may be prescribed on its own or in combination with sulfasalazine and/or hydroxychloroquine and/or leflunomide. DMARDs can take several weeks to ‘work’ or become effective and for a short period, treatment with a steroid as well may be required as mentioned earlier as a ‘bridging’ therapy ie to give symptom relief while waiting for the DMARDs to 'kick in'. It is important to 'hit' the disease hard in the early stages to bring it under control as quickly as possible. For more information about combination therapy visit our website at www.nras.org.uk. Some people experience side effects from DMARDs but it is important to emphasise that the effects of uncontrolled disease are worse overall than dealing with the side effects of medication.

However, it must be acknowledged that some people may require several different treatment combinations before good control of their RA is achieved. Some drugs will not work at all and some will work for a limited period only. The decisions on eligibility for the biologic or biosimilar drugs are influenced by many factors, not the least of which is funding. Turn to P.18 and 19 for more on the eligibility criteria for being prescribed biologic and biosimilar drugs.

You will see from this booklet there are different options available to treat RA and if one medication doesn’t work or the side effects are too difficult to overcome there will be alternative drugs which can be considered. But, taking your medication regularly in accordance with the prescribed dosage – which is known as adherence – is
vitaly important if you want to get your disease under control, prevent joint damage and get on with living your life to the full.

Complementary/alternative therapies

There is no complementary or alternative treatment which can control your disease. If there were, we would know about it! However, we are aware that many people want to try complementary therapies for the relief of symptoms but we recommend that you tell your rheumatology team who will support and advise you. Remember even if something says "natural" or "herbal" they still may have an interaction with your prescribed medication.

Blood tests will be carried out on a regular basis to pick up any effects that the drug/s are having. While it is understandable to be worried about side effects of medications it is important to not be excessively so. Controlling the disease is the most important thing! If you want to talk to someone else who has RA and is on the same treatment as you, call our helpline on 0800 298 7650 to arrange a call from one of our trained Volunteers (Mondays to Fridays, 9.30am to 4.30pm).

Adherence: keep taking the treatment for good control of your RA

It is really important to emphasise the fact that when RA is treated effectively and as soon after the start of symptoms as possible, the long-term outcome (a good and full life) is more likely to be possible. We can’t emphasise enough how important it is to take your prescribed medication regularly and exactly as prescribed (ie correct dosage); however, we do acknowledge that it’s easy, especially when you are feeling well, to forget. Also, if you are suffering side effects, you may not
want to take your medication. Evidence suggests that people with RA take their treatment between 30% and 80% of the time but do not tell their doctors when they miss a dose. Good control is reliant on taking the medicine. Without it, you risk flares of your disease, ongoing pain and stiffness, joint damage and disability.

The following extracts from published papers about non-adherence (failing to take the medicines as prescribed) are very significant and include the evidence for worsening of disease:

“Medication non-adherence not only leads to substantial worsening of diseases and illnesses, in many instances it causes repeat visits to GP surgeries and hospitals.”

“If you look at all the major chronic illnesses, every one of them needs good medication adherence in order to keep them under control.”

“Non-adherence is a big problem. When patients don’t feel ill they think there is no need for them to take their drugs any more. Or, if they start to feel better, they arbitrarily decide they don’t need to take as much. But many of these patients have chronic diseases and will be on drugs for the rest of their lives.”

“Patients may forget their treatment or actively decide not to take it for a host of reasons. It can be hard to discuss these issues during a busy clinic appointment and it takes time and courage to raise these concerns. Building a two-way relationship of honesty, openness and respect for the clinician and the patient will be really beneficial. Patients should feel empowered (able) to recognise why they are struggling and try to find the courage to articulate (speak about) the concerns that dominate their treatment decisions; seeking help from family, friends, GPs and NRAS can be invaluable here.”

Your rheumatology team are sympathetic to reasons for not taking your medication, so please do discuss your situation honestly so they can help you.

What is the Treat to Target pathway?

Rheumatologists help those with RA to achieve the best possible control of their condition using the guidance of a pathway of care called ‘Treat to Target’ (T2T). The T2T pathway offers a simple, visual guide for treating RA as a logical step-by-step procedure. The aim is to achieve the best results possible for each individual with RA.

The process indicates two targets: the main target of remission (leading to sustained remission); and the alternative target of low disease activity.

Although there are two paths to target, the approaches to them are essentially identical. Monitoring each patient regularly and recording the details of each step is vital. This way the treatment therapy can be adapted to individual patients’ needs to achieve their own personal target. The treatment of RA must be based on a shared decision and agreement between the patients and their rheumatologist.
The Treat to Target pathways

(The ‘composite measure of disease activity’ mentioned in the diagram refers to DAS28, which is explained in more detail below.)

Measuring disease activity: DAS28

Rheumatology health professionals measure disease activity in patients with RA by calculating a Disease Activity Score (DAS 28). For each person with RA, the test involves examining 28 joints to see if they are swollen and/or tender and combining this with blood test results and an overall health score.

You can find out more about DAS 28 from www.nras.org.uk/das28, where there is both a patient guide to DAS 28 and guidance on how to download the free 'Know your DAS' app for most mobile phones and tablets.
Why is keeping RA under tight control important?

The benefits of ‘tight control’ in the management of RA are now widely accepted. Professor Peter Taylor explains.

The faster we can switch off harmful inflammation in RA, at every stage of the disease, the better the outcomes are for patients in terms of quality of life and prevention of joint damage. Even if you were diagnosed many years ago, the more the inflammation can be suppressed now, the better you will do. What matters is to keep the total amount of inflammation you experience over time as low as possible. The ideal goal is for patients to achieve remission, or low disease activity if remission is not possible. That’s the aim of tight control, and it can benefit everyone with RA although it gives optimum benefit when started as early as possible in the disease course of RA.

So what does ‘tight control’ mean, in practice? The principles are that your disease activity is assessed by regular monitoring and that treatment is stepped up when there is still evidence of ongoing disease activity. Clinical assessment ideally needs to be frequent (every one to three months) when treatment is first initiated. If there is no improvement by, at most, three months after treatment start, or the target has not been reached by six months, therapy should be adjusted. Once the treatment target is achieved, progress check-ups can become less frequent, maybe every six to eight months. If your disease remains active or flares after an initial improvement, then you may be assessed more often, and your treatment escalated until it settles down. However, it must be remembered that RA is different for everyone and each person will be invited to discuss their individual treatment plan with their own healthcare team.
Tight control can involve using disease modifying anti-rheumatic drugs (DMARDs) in combination as well as singly. We now know that in the majority of cases, combination therapy achieves tight control with few additional side effects or complications by comparison to mono-therapy (using one DMARD on its own). If conventional disease modifying drugs do not allow the treatment target of either remission or low disease activity to be reached, then you may be an eligible candidate for a biologic (or biosimilar) disease modifying drug. However, because of the expense of these treatments, in the UK there are eligibility rules to meet, before being able to receive treatment with a biologic or biosimilar, that are determined by NICE (in respect of England and Wales) and/or (in Scotland) the Scottish Medicines Consortium (SMC) – P.18-19.

As with every drug, your rheumatology team will discuss the range of treatment options with you with a view to achieving the best outcomes with the lowest risk of any side effects from drugs

Although it is good to switch off harmful inflammation, it is not desirable to prevent the body’s natural ability to fight infection and to protect us from the environment we live in. But overall, tight control with escalation of treatment leads to better outcomes and this has become a guiding principle of treatment.

If disease remission has been achieved and maintained for a long time, in some cases it may be appropriate to reduce the amount of medication that you are taking. Your rheumatologist will discuss this with you if appropriate. But you should not reduce treatment yourself without consultation, or just because you are feeling better!

There is always a risk that this could lead to a flare and your rheumatology team will want to work together with you to ensure that your treatment regimen is the one best suited to your unique needs.

Suddenly my RA is much worse – is my treatment failing? (Recognising and managing flares)

During the early stages of managing your condition, learning about RA in more detail and gradually getting used to the treatment regimens (the appointments with doctors and other health care professionals), you may find yourself inexplicably feeling tired or even exhausted, in pain and possibly with one or more swollen joints. This is very likely to be a ‘flare-up’ of your RA and can happen from time to time for people during the course of their disease without any apparent warning, even if you’ve had the disease for many years.

A flare is any worsening of disease activity that might, if it persists, need a specialist’s review and possibly a change of therapy. A flare can last for anything from one day to several days or sometimes longer.

The following summary is to help you understand how to recognise a flare
and how to look after yourself as well as possible during a flare:

- Learn as much about RA as you can so that you feel you are able to manage the good and not so good days with understanding. For more information on our range of self-management programmes, refer to our website
- Learn how to manage pain (P.22)
- Fatigue or extreme exhaustion is a common problem
- Try to find the reason for your flare. There may be no obvious cause that you can find but sometimes there are ‘triggers’ such as:
  - any situation that for you is stressful, either physically or emotionally
  - an apparently minor infection
  - a break in your medicines routine (see Adherence: keep taking the treatment for good control of your RA, P.11 above)
  - becoming severely tired by overdoing activities. Knowing how much your body can handle will help
  - overusing certain joints – for example, your hands after prolonged hard work that causes swelling and pain in the joints
  - certain weather conditions, such as humidity or cold weather, may make the joint discomfort more obvious
  - if you have a flare-up that just does not go away, it may be a sign that your RA is not fully controlled by the medicines as prescribed and you need to be reassessed by your rheumatology team for more effective control

Ways to ease the symptoms of a flare:

- take pain relief medication as prescribed regularly
- try to balance your activities with plenty of rest so that your joints and your body can relax – this is called ‘pacing’ yourself (in other words, don’t overdo it!)
- consider the possible cause for your flare and try to be kind to yourself
- use cold relief such as cold water or ice packs (wrapped up) on the swollen joints several times a day or warmth such as warm water, heating pads or a warm bath. Alternating cold and warm treatments can also be helpful
- a light range of motion exercises, which simply means moving all the joints through their normal range of movement is recommended
- some stress-management activities may be appropriate, such as yoga, deep breathing, meditation
- during a flare, assistive devices like a piece of foam round a pen or knife to widen the grip, a long ‘grabber’, a stick or crutch may help to keep you coping and moving
- you may feel that a check-up with your rheumatology team is needed to review the treatment regimen, or that your GP might be able to help, but remember that a flare is usually temporary and not a permanent change in your RA
A flare can have a temporary impact on your ability to work. Whether your employer knows your medical situation or not is a personal decision but with the right support from your employer, your rheumatology team and patient support groups, many people find that any problems in the workplace can be successfully managed.

NRAS has two useful booklets ‘I Want to Work’ for employees, and ‘When an Employee has Rheumatoid Arthritis’, for employers.

Self-management: helping you to manage your RA more effectively

Initially, everyone will need help to begin to feel sufficiently supported and able to cope with their RA.

The aim of self-management is to manage your RA, your treatments and day-to-day life in the best possible and most realistic way to suit your lifestyle.

It’s not about ignoring or denying a health condition, nor is it about allowing that condition to dominate your life, but instead it offers a much more constructive way of living that has been shown to improve long-term outcomes.

In practice, what this means is that by having a helpful understanding of the condition, being able to recognise and manage the emotional impact and willing to make adaptations to your lifestyle and the way you approach doing things, you can take back control of your life and get into the driving seat again.

When you have a condition like RA, you’re already managing it in lots of ways, but there are also specific skills you can learn, to gain more confidence and knowledge. Becoming a good self-manager takes time and practice; it’s rather like learning any other skill, such as driving a car or playing a musical instrument. With some simple skills you
can become an effective self-manager who feels confident to make the decisions and changes which can affect your health in a positive way.

Everything we do as an organisation is about providing resources and support to enable people to self-manage effectively. Our helpline, our peer-to-peer support service, our community groups, our self-management programmes and our many publications are there to help you understand and manage your disease as well as possible. Do get in touch with us (see the back cover of this booklet for all our contact details). Your rheumatology specialist nurse and other members of your healthcare team can help with information about your condition, treatment and medication and signpost to our resources. They can offer support, particularly when things change or when you have a flare-up, so make sure you know the nurse helpline number at your hospital.

**Approvals and funding for treatment**

New drugs and treatments are assessed by the National Institute for Health and Care Excellence (NICE) and the Scottish Medicines Consortium (SMC). When NICE or the SMC passes a drug for use in the NHS, the local Clinical Commissioning Groups (England) and Health Boards (Wales, Scotland and Northern Ireland) must fund treatment for people who meet the eligibility criteria, usually within three months (except in Northern Ireland) of the decision being made public.

**NICE** National Institute for Health and Care Excellence

[www.nice.org.uk](http://www.nice.org.uk)

NICE is responsible for providing national guidance on promoting good health and on preventing and treating ill health. It produces guidance in three areas:

- **public health** – guidance on the promotion of good health and the prevention of ill health for those working in the NHS, local authorities and the wider public and voluntary sector
- **health technologies** – guidance on the use of new and existing medicines, treatments and procedures within the NHS. In this area it publishes Technology Appraisals (recommendations on the use of medicines and treatments) and Interventional Procedures (procedures used for diagnosis or treatment, for example surgical procedures)
- **clinical practice** – guidance on the appropriate treatment and care of people with specific diseases and conditions within the NHS. In this area it publishes Clinical Guidelines (recommendations on appropriate treatment and care)

NICE guidance is developed using the expertise of the NHS and the wider healthcare community including NHS staff, healthcare professionals, patients and carers, industry and the academic world. This guidance determines what the NHS will fund, and it sets out the standards of care that patients can expect.
Assessment of new biologic drugs by NICE comes under the heading of Technology Appraisals. (Note: NRAS has provided lay expert patients for all NICE Technology Appraisals in respect of drugs for RA since 2003)

The table below sets out where the different types of NICE guidance apply in the UK.

* with advice on implementing in the context of the health service in Northern Ireland from the Department of Health, Social Services and Public Safety

** only multiple technology appraisals, with advice on implementing in the context of the health service in Scotland from NHS Quality Improvement Scotland

The SMC is the equivalent of NICE in Scotland. It provides advice to NHS Boards and their Area Drug and Therapeutics Committees (ADTCs) across Scotland about the status of all newly licensed medicines, all new formulations of existing medicines and new indications for established products (licensed from January 2002). It makes advice available as soon as practical after the launch of the product involved. It also carries out ‘horizon scanning’. It aims to improve financial and service planning within NHS Boards by providing them with early intelligence about new medicines in development.

NB: The SMC follows NICE guidance in Multiple Technology Appraisals, that is, where more than one drug is being considered. Where only one drug is being evaluated – Single Technology Appraisals – these go through the SMC, who conduct their own evaluations.

### NICE Guidance in the UK

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cover all the other lifestyle and non-medicine based support and treatment available.
Medications for the treatment of RA

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Managing Pain

Pain is an extremely personal experience. All pain that is present for a reasonable length of time, no matter what the underlying cause, can be associated with poor sleep patterns and low or depressed mood.

The stress associated with RA-related job issues or relationship or family problems all impact on how we cope with pain. Pain involves not only the nerves at the site of the pain but the nerve pathways leading to the brain and special pain pathways within the brain itself. Very simply, pain is a complex issue.

The best way to ease the pain of RA is to aim for effective and continuing control of the disease process. This is with management of the disease by the various medicines outlined in this booklet. Immediate relief from pain can be achieved by taking simple painkillers, combined pain remedies. Non-steroidal anti-inflammatories or in some situations, steroid preparations

<table>
<thead>
<tr>
<th>Type</th>
<th>Examples</th>
<th>Purpose</th>
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<tbody>
<tr>
<td>Analgesics also known as painkillers</td>
<td>Paracetamol, Co-Dyrdramol (Paracetamol and Dihydrocodeine), Co-Codamol (Paracetamol and Codeine Phosphate), Tramadol (strong painkiller and mild opioid)</td>
<td>To help control pain</td>
</tr>
<tr>
<td>Non steroidal anti-inflammatory drugs (NSAIDs)</td>
<td>Ibuprofen, Meloxicam, Diclofenac, Naproxen</td>
<td>To ease pain and stiffness by reducing inflammation but NSAIDs do not prevent future damage</td>
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<tr>
<td>Corticosteroids also known as steroids</td>
<td>Prednisolone</td>
<td>Reduce inflammation, thereby relieving pain. Usually prescribed as tablets. Can be given as a ‘rescue remedy’ (as a course of tablets) during a severe episode of RA</td>
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<tr>
<td></td>
<td>Methylprednisolone</td>
<td>Can be injected into muscle or joints. Can be given as a ‘rescue remedy’ as an intra-muscular injection</td>
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<td>Triamcinolone-acetonide, Triamcinolone-hexacetonide</td>
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may be prescribed as well to give relief when the swelling and inflammation are excessive.

When is the best time of day to take painkillers?

This decision depends on the time of day that the pain might be at its worst, either early morning, as the day progresses or throughout the day or before bed, to help manage the pain overnight. Your decision will also be guided by the time your particular medicine takes to be effective and the duration of its effect.

Remember that the non-steroidal anti-inflammatories (NSAIDs) cannot be taken on an empty stomach, only after a meal or a small amount of food, meaning that they must not be taken last thing at night. Your GP may prescribe stomach protection medication whilst you are taking NSAIDs.

NSAIDs explained

- Anti-inflammatories work in two ways: to relieve pain; and to reduce inflammation (swelling, redness, heat and pain)
- To reduce pain, the effect from the prescribed NSAID dose taken with or after food may be felt after the first dose. It can take a week to achieve complete pain relief
- To reduce inflammation (the swelling in the joints) a regular dose must be taken (with or after food) thereby keeping a constant level of the drug in the blood stream and the full benefit in reducing swelling may take up to three weeks
- Occasionally, NSAIDs may take longer than three weeks to be fully effective in controlling the swelling, redness, heat and pain. If necessary, an alternative NSAID may be required for improved control of symptoms
- NSAIDs should only be used for the shortest possible time

Which drug is prescribed?

There is very little difference between the NSAIDs and the way they work but individuals can have considerable differences in the way they respond to them.

- Ibuprofen combines the benefits of pain relief, reduction of inflammation and lowering of fever. It has fewer side effects than other NSAIDs but its anti-inflammatory properties are weaker
- Naproxen is an effective NSAID which is well tolerated
- Diclofenac is similar to Naproxen
- Indomethacin is a little more effective than naproxen but has a high incidence of side effects that include headache, dizziness, and gastro-intestinal disturbance
- Piroxicam is as effective as naproxen but works for longer so that one dose daily is effective. It has more gastro-intestinal side effects and can cause frequent skin reactions
- Meloxicam may be prescribed for long term treatment of RA and is a once daily medicine
Prescribing precautions

- Prescribing doctors will be aware of the precautions they need to take in their choice of NSAID
- It is vitally important that patients inform the doctor of all the information needed to prescribe safely. This includes information about any other diagnosed medical conditions and medicines currently prescribed (particularly heart or kidney disease, asthma or blood disorders)
- NSAIDs must only be taken with or after food because of the irritant effect they can have on the stomach
- The dose range for each NSAID is specific to the individual drug and therefore the dose of one cannot be compared to another
- Antibiotics containing trimethoprim are avoided when NSAIDs are being taken
- When NSAIDs are given as well as methotrexate the dose of methotrexate should be carefully monitored. This is rarely a clinical problem

Most commonly reported side effects

As with any medication, NSAIDs have a number of possible side effects, although it is important to remember that these are only potential side effects. They may not occur at all.

The potential side effects listed below cover all the NSAIDs in the previous section. Ibuprofen, naproxen and diclofenac have the least side effects, with the risk of side effects increasing in the subsequent 3 NSAIDs.

- Gastro-intestinal disturbances include discomfort, nausea, diarrhoea, and occasionally bleeding and ulceration. During longer term use stomach protection will be prescribed such as omeprazole or lansoprazole
- Hypersensitivity reactions such as rash, bronchospasm (mimicking asthma), angioedema (swelling of lips, tongue, around the eyes)
- Headache, dizziness, nervousness, hearing disturbances such as tinnitus (ringing in the ears), sensitivity to sunlight and blood in the urine
- NSAIDs have the potential to worsen asthma, but this will be checked by your specialist or GP
- There are other rare but potentially serious side effects and these are listed in the specific patient information leaflet in the packaging
- In people with any kind of existing heart disease, caution would be taken in the prescribing of an NSAID
Steroids

Steroids are also known as corticosteroids or glucocorticoids. They are used to help control many forms of arthritis.

Steroids are naturally occurring chemicals produced from the two adrenal glands, which lie above the kidneys. During the day, when people are active, there are more glucocorticoids produced naturally.

The glucocorticoids are composed of cortisone and hydrocortisone and these control metabolism. Metabolism is the sum of the physical and chemical processes within the body that allow for growth, function, repair of tissues and provision of energy.

Steroids used by body builders are gonadocorticoids or anabolic steroids. These steroids are variations of the male sex hormone testosterone, first created by pharmaceutical companies in the 1950s and therefore not the same as steroids taken in RA.

Background

Cortisone was used for the first time for rheumatoid arthritis in the late 1940s. In 1950-51 cortisone and hydrocortisone were developed as tablets and joint injections. By the 1960s, all the side effects of steroid use had been reported.

The development of non-steroidal anti-inflammatory drugs (late 1950s) enabled the steroid doses to be lowered and used much more for short courses.

By the 1970s, the introduction of methotrexate had a significant impact on controlling rheumatological conditions while also allowing further reductions in steroid doses and use of short courses – although the widespread use of methotrexate didn’t really happen until the early-to-mid 1980s.

Facts about steroids

- Steroids can be taken as tablets or injected or by infusion (a ‘drip’)
- In the average adult, all the cortisone and hydrocortisone (the steroids made naturally in the body, as outlined above) produced in 24 hours would add up to the same amount of steroid (glucocorticoid) as approximately 5-6 mg of prednisone or prednisolone medication
- A low dose of a steroid medication such as prednisolone will have a noticeable effect within a few days. Joint pain, stiffness and swelling will be less. A large dose will have a larger and quicker effect. Very large doses given as a one-off injection into the muscle can often provide a quick improvement that can sometimes seem miraculous
- Steroids can make you feel better in yourself and can provide a sense of wellbeing
When are steroids used?
Steroids are used sparingly for conditions such as RA, because of the side effects, in the smallest possible dose for the shortest time. They can be very useful at the start of treatment either as a joint injection or an occasional intra-muscular or intra-venous dose.

A helpful article on steroid joint injections can be found at: www.nras.org.uk/4-tests-treatments-and-information

- Steroids can be very effective in treating a ‘flare up’ of RA by controlling the symptoms quickly
- Steroids are used with caution and the doctor will have various considerations before prescribing the drug
- When reducing a steroid dose, your doctor will recommend a very gradual reduction over time which allows your body to re-adjust to producing steroid naturally.

What are the possible side effects of tablets used for a short time or injections into a muscle or vein?

Mild effects may include:
- Red flushing of the face which does not last
- A metallic taste in the mouth
- Hyperactivity
- Tiredness
- Mood changes
- Blurred vision

Rare effect with an infusion into a vein:
- Hypertension (raised blood pressure) which usually settles by slowing down the rate of infusion

Extremely rare effects:
- An altered level of consciousness
- An altered state of mind
- Seizures

What are the rare side effects of joint injections?
- The potential risk of a joint infection can be a direct result of the injection (with good techniques this is very rare)
- Red flushing of the face which does not last
- Slight swelling of the face giving it a rounded appearance
- An increase in calcium deposited around the joint injected
- Adults who also have diabetes may need an increased dose of insulin for a short time following a joint injection (this is always explained fully at the time)
- Near the site of an injection of a small joint there may be a small depression in the skin where the underlying fat is affected. This can result in a slight change of skin colour (this may be seen near a wrist or knuckle injection)
- Pain following an injection is rare, but should be helped by paracetamol
What are the possible side effects with long-term use of steroids?

- If steroids need to be used for longer than a month or in slightly higher doses than the generally accepted 'low dose regimen' it is likely that the immune system will be suppressed. This is called 'immunosuppression'.

- Be aware that taking steroids can suppress or mask the effects of an infection. It is better to get advice at the first indication that an infection is starting than to 'wait and hope' that it will come to nothing. Be safe!

- Rarely, there is a possibility that a number of side effects could develop such as diabetes, thinning of the bones (osteoporosis) and weight gain which might show as a rounded face.

- Remember that the consultant specialist will be very aware of these possibilities, will discuss them fully and will make every effort to control the RA without risking long term problems.

Steroids and immunisation/vaccination

- It is recommended that protection against pneumococcal infections is important. These can lead to pneumonia, septicaemia or meningitis. Protection is best given before steroids begin but it is possible for this immunisation to be given during low dose steroid treatment.

- The annual flu vaccination is also recommended.

- In general, if you are on steroids, immunisation is only possible with a 'low dose regimen' of steroids. There is no evidence that immunisation will worsen RA.

- For anyone who is ‘immunosuppressed’ (meaning with a reduced immune response) live vaccines cannot be given. These are measles, mumps, rubella (MMR), chickenpox, oral polio (NOT injectable polio), BCG, oral typhoid and yellow fever. If steroids have not yet been started it is important to seek advice on how long a gap to leave after having a live vaccine.

Additional important advice

If a steroid treatment has been taken for three weeks or more it needs to be reduced gradually on the advice of the doctor in charge of the treatment, rather than stopped abruptly.

A steroid card needs to be issued at the start of treatment and carried by the patient at all times.

For those who may be in contact with chickenpox or another infectious disease, or who have become ill with an infection, it is important to speak to your doctor as soon as possible for advice.
Methotrexate

Methotrexate is ranked as the ‘gold standard’ disease modifying anti-rheumatic drug (DMARD) for the control of inflammatory arthritis.

The over-active immune system in RA causes pain, swelling, heat and redness in the joints, stiffness and other symptoms such as fatigue and flu-like symptoms. Methotrexate dampens down this process, it reduces the evidence of active arthritis and the potential for joint damage.

Background

- Methotrexate (MTX) was introduced in 1947 and was initially used to treat leukaemia and other forms of cancer
- From the 1980s, methotrexate was used to treat adults with RA but in very much lower doses (than doses used for leukaemia and cancer) after clinical trials had demonstrated its benefits in RA
- Although this booklet is for people with RA, it’s reassuring to know that from the 1990s methotrexate has been used in children and young people with juvenile idiopathic arthritis
- Research into RA has found that the earlier the treatment starts with a DMARD to control the inflammation, the better the long term outcome

How does it work?

It has not been possible to identify the precise mechanism within the cells for the effectiveness of methotrexate.

It is vital to remember that methotrexate is prescribed as a ONCE weekly dose in order to avoid any possible overdose. It is recommended to take methotrexate on the same day each week.

It is available as:

- Tablets
- A subcutaneous injection (just under the skin) via a pre-filled pen device

Advice and guidance will always be given. In addition, the rheumatology team will advise on the dose and frequency of folic acid (a ‘B’ vitamin) supplementation (see below for more details).

Injectable methotrexate (using pens or syringes) needs to be kept below 25 degrees centigrade and protected from light, but it doesn’t need to go in the fridge.

Most commonly reported side effects

As with any medication, methotrexate has a number of possible side effects, although it is important to remember that these are only potential side effects. They may not occur at all.

Side effects may include:

- Nausea, loss of appetite, vomiting, diarrhoea
- Mouth ulcers, skin rash
• Effects on blood tests for liver function, white blood cell and platelet numbers
• Headaches
• Mild hair loss
• Fever, symptoms of infection, bruising, bleeding
• Rarely shortness of breath and troublesome cough causing pneumonitis which is inflammation in the lungs
• Photosensitivity (increased sensitivity to sunlight)
• Mood swings (not common)

More information on side effects can be found in the patient information leaflet for methotrexate, which will come with your medicine.

Remember to report any concerns about possible side effects to the doctors, pharmacists or nurses.

Methotrexate with other medicines
Methotrexate interferes with the absorption of B vitamins, such as folic acid, from the diet. Because of this, a supplement of folic acid is usually prescribed but MUST NOT be taken on the same day as methotrexate.

Folic acid:
• is needed for normal cell division, especially in infancy
• is needed in the production of red blood cells

• must be taken on a separate day from the weekly methotrexate

The antibiotics co-trimoxazole and trimethoprim should not be taken whilst on methotrexate.

Additional disease modifying anti-rheumatic drugs (DMARDs) or biologic medications may be prescribed in conjunction with methotrexate.

Remember to take care when using any other medications or complementary therapies (even if bought ‘over the counter’ for colds or flu). Remember to check with your doctor, nurse or pharmacist that they are safe to take with methotrexate and any other medication taken.

Methotrexate and pregnancy
• Methotrexate may harm the growing baby and cause birth defects. It is therefore important to avoid pregnancy when taking methotrexate
• Contraception is important and oral contraceptives can be taken with methotrexate
• Teenage and adult men should not father a child whilst they are taking methotrexate

Before starting a family it is recommended that you get advice from the consultant or clinical nurse specialist about when it is safe to start a pregnancy (generally three to six months from the last dose taken). This advice applies to both men and women.
Methotrexate and alcohol

If drinking alcohol, it is important to discuss how to drink safely whilst on methotrexate with the specialist team, as both alcohol and methotrexate are processed in the body by the liver. If the liver is working too hard, this will show up on the liver function tests. The following tips may help:

- Discuss with your rheumatology team about drinking safely, know what the government guidelines are
- Your consultant/clinical nurse specialist will advise you about safe alcohol consumption
- Get an understanding of units of alcohol and recommended daily limits. Visit www.nhs.uk for more information. The size and strength of your drink determines the number of units of alcohol it contains
- The higher the alcohol by volume (ABV) of a drink, the higher the proportion of alcohol it contains. For example, a drink with an ABV of 13 contains 13% pure alcohol
- Limit the amount of alcohol by drinking drinks with a lower alcohol content
- Avoid binge drinking
- Have alcohol-free days
- Avoid having blood tests the day after drinking the night before as this can affect blood monitoring

Methotrexate and immunisation/vaccination

Live vaccines (measles, mumps, rubella ie MMR, chickenpox, oral polio (NOT injectable polio), BCG, oral typhoid and yellow fever) cannot be given to anyone already taking methotrexate. If methotrexate has not yet been started, it is important to seek advice on how long a gap to leave after having a live vaccine.

- The annual flu vaccination and ‘pneumovax’ protection against pneumonia is permitted (see below)
- If possible the ‘pneumovax’ vaccination should be given before starting methotrexate

Flu vaccine is now available in two forms, an injection for adults and a nasal spray for children. The injection is not a live vaccine and therefore suitable for adults taking methotrexate and is recommended. The nasal spray is a live vaccine and not suitable for adults taking methotrexate. It is important to discuss having a flu vaccination with your GP.

Vaccination of close family members can help to protect someone with a lowered immune system from infection.

Methotrexate and chickenpox

- Before methotrexate is started, a blood test to check for immunity to chickenpox is advisable. Ideally, a chickenpox vaccination would be given before starting methotrexate, but this would cause a delay in commencing treatment. The consultant or clinical nurse specialist will discuss whether such a delay is acceptable
Anyone taking methotrexate who comes into contact with chickenpox – and this means being in the same room as someone with chickenpox for 5 minutes or more – should seek advice. This is because they may require an injection of VZIG (Varicella-Zoster Immune Globulin) for protection which is their doctor’s assessment and decision.

How to reduce methotrexate-related nausea

To help the feeling of nausea, one of the more common side effects of methotrexate, it is recommended that methotrexate is taken (or given) after the evening meal so that the nausea will therefore be less on waking. The most appropriate day for the individual needs to be considered.

Folic acid is important as explained above, but it also helps to reduce the nausea.

Anti-nausea medication may also help.

Stay safe on methotrexate and remember to have regular blood tests and check-ups as advised by your consultant and clinical nurse specialist.

Injected methotrexate can improve the side effects of taking tablets, so if you are experiencing side effects, ask about sub-cutaneous methotrexate.

Hints and tips

Prevention of sunburn

- **Remember** to use sunscreen before going into the sun, as well as a t-shirt and hat.

Reapply sunscreen frequently as recommended.

**Travelling and methotrexate**

- **Going by air (flying)**
  - Inform the airline if injectable methotrexate has to be carried on the flight.
  - Injectable pens or syringes need to be kept below 25 degrees centigrade and protected from light. These may need to be carried in hand luggage, together with a letter of authorisation to carry needles or injectable pens from your healthcare team.
  - It is a good idea to take a copy of the prescription to show authorities.

- Before booking a holiday, live vaccines must be avoided (see above ‘methotrexate and immunisation/vaccination’). It is important to check whether any required vaccines are ‘live’.

Due to the fact that methotrexate (MTX) is the gold standard treatment in RA and many thousands of people are prescribed MTX at diagnosis, we are regularly contacted by people who may be anxious about taking it. We therefore felt it was important for us to have listed the possible side effects of MTX – and equally important for us to emphasise here that, with regular blood monitoring, there is good safety data and evidence that it is a safe and effective treatment for many people with RA.
Sulfasalazine

Sulfasalazine is known as a disease modifying anti-rheumatic drug (DMARD).

In the gut sulfasalazine is broken down (by the normal gut bacteria) into two parts: one part a sulphonamide antibiotic which kills harmful bacteria; and a second part which acts to reduce the process driving inflammation as well as helping to control the overactive immune system.

This overactive immune system in RA is the cause of swelling, pain, heat and redness in the joints and other associated symptoms such as fatigue and generally feeling unwell.

Sulfasalazine may be prescribed as a single DMARD or prescribed at the same time as another DMARD. It is frequently prescribed in combination with methotrexate.

Background

- Sulfasalazine was introduced in the 1950s, initially to treat inflammatory bowel disease, but also for the treatment of rheumatoid arthritis (RA) as it was believed then that bacterial infections were the cause of this form of arthritis
- Following positive results from clinical trials in the late 1970s it was used more extensively in RA and subsequently used for some forms of juvenile arthritis (but not extensively)
- Sulfasalazine is also used to treat inflammatory bowel disease, ulcerative colitis and Crohn’s disease

How long does it take to work?

- Sulfasalazine is available in liquid form or tablets
- The daily dose of sulfasalazine is gradually increased each week, usually for three weeks, until the maximum prescribed daily dose has been achieved
- Controlling the symptoms of RA with sulfasalazine may take up to three months or longer

Most commonly reported side effects

As with any medication, sulfasalazine has a number of possible side effects although it is important to remember that these are only potential side effects and may not occur. Side effects that can occur will be experienced during the first three to six months. These include:

- Nausea (feeling sick), vomiting, dizziness, headache, diarrhoea, loss of appetite
- Skin rash, raised temperature, insomnia, itching of skin, tinnitus
- Bruising, sore throat, mouth ulcers, cough
- Effects on the blood tests, including the blood cell count, the blood chemistry and liver tests and
measures of inflammation (using tests known as ESR and CRP)

• Yellow/orange discoloration of the urine, protein in urine (proteinuria)

• For young men, reduced sperm count whilst on the drug, reversible on stopping

**More information on side effects can be found in the patient information leaflet for sulfasalazine.**

**Remember to report any concerns about possible side effects to the doctors or nurses.**

**Sulfasalazine with other medicines**

• Sulfasalazine may interfere with the absorption of folic acid (one of the B vitamins) from the diet. If methotrexate is prescribed as well as sulfasalazine the regimen for a weekly supplement of folic acid will be required

• Sulfasalazine may reduce the absorption of some heart drugs

• Sulfasalazine must not be prescribed if you are sensitive to sulphonamides or aspirin

• If you are taking sulfasalazine, do not buy any other medicine or remedy (eg for colds or flu) without first consulting your doctor, nurse or pharmacist

• **Remember** to take care when using any other medications or complementary therapies (even if bought ‘over the counter’ for colds or flu). Remember to check with a doctor, nurse or pharmacist that they are safe to take with sulfasalazine and any other medication taken

**Sulfasalazine during pregnancy and breast-feeding**

• If sulfasalazine is to be prescribed during pregnancy an analysis of the risks and benefits to the mother should be undertaken, against the possible small risk to the unborn child

• Folic acid supplementation is required whilst trying to conceive and during pregnancy, and should be discussed with your doctor

• Breast-feeding is not advisable when taking sulfasalazine

• Young men should be aware that although sulfasalazine lowers the sperm count, contraception is still recommended to prevent an unplanned pregnancy. The lowered sperm count is reversed when you stop sulfasalazine

**Sulfasalazine and alcohol**

Alcohol can be consumed when taking sulfasalazine. However, caution may be required when taking other medications alongside this drug, for example methotrexate.

**Sulfasalazine and immunisation/vaccination**

If you are taking sulfasalazine, immunisations and vaccinations can be given if required.
Advice should be sought from your prescribing doctor regarding chickenpox vaccination before starting treatment and if the person taking sulfasalazine comes into contact (defined as five minutes or more in the same room) with chickenpox, without having immunity to the disease.

Live vaccines (measles, mumps, rubella (MMR), chickenpox, oral polio (NOT injectable polio), BCG, oral typhoid and yellow fever) cannot be given to anyone already taking sulfasalazine. If sulfasalazine has not yet been started it is important to seek advice on how long a gap to leave after having a live vaccine.

Flu vaccine is now available in two forms, an injection for adults and a nasal spray for children. The injection is not a live vaccine and therefore suitable for adults taking sulfasalazine and is recommended. The nasal spray is a live vaccine and not suitable for adults taking sulfasalazine. It is important to discuss having a flu vaccination with your GP.

Vaccination of close family members can help to protect someone with a lowered immune system from infection.

Hints and tips

- Stay safe on sulfasalazine by remembering to have regular blood test monitoring as advised by the consultant or clinical nurse specialist
- Remember that contraception is still required if men taking sulfasalazine do not wish to father a child even though the sperm count is likely to be lowered
Hydroxychloroquine

Hydroxychloroquine is a treatment for malaria but has been shown to have an effect on the messaging system between cells by interrupting the inflammatory response. It is this mechanism that is beneficial in both RA and juvenile idiopathic arthritis (JIA).

Hydroxychloroquine has been available since the 1970s and is used widely for the treatment of lupus (SLE) but is also an established drug for the treatment of mild RA. It is commonly used in combination with one or two other disease modifying anti-rheumatic drugs (DMARDs), particularly methotrexate.

**Background**

- Hydroxychloroquine was first developed as the drug 'chloroquine' to treat malaria
- Chloroquine was modified to hydroxychloroquine to significantly reduce the possible side effects that were causing eye problems

**How does it work?**

- Hydroxychloroquine is only available as a 200mg tablet
- The action of hydroxychloroquine is not fully understood and it is a cumulative effect over several weeks before any benefit is seen
- Blood tests for hydroxychloroquine are checked before treatment starts and then as frequently as the specialist advises, usually at clinic visits. When it is prescribed alongside other DMARDs the frequency of blood tests may be more regular, depending on the recommendations for the other DMARD(s)

**Most commonly reported side effects**

As with any medication, hydroxychloroquine has a number of possible side effects, although it is important to remember that these are only potential side effects and they may not occur at all. Side effects may include:

- Loss of appetite, anorexia
- Headache
- Skin reactions – rash, itching, photosensitivity (increased sensitivity to sunlight)
- Visual changes – blurring*
- Abdominal pain, cramps, nausea
- Diarrhoea, vomiting
- Blood disorders
- Risk of episodes of low blood sugar levels in patients with diabetes

* The Royal College of Ophthalmologists has reviewed screening for visual side effects to hydroxychloroquine and these are very rare. Vision should be checked prior to the start of treatment and
corrective spectacles prescribed if required. During treatment any visual symptoms need to be checked annually. Referral to an ophthalmologist is required if any changes are detected.

Please note: over-dosage is very dangerous, particularly in small children.

More information on side effects can be found in the patient information leaflet for hydroxychloroquine that comes with your medicine.

Remember to report any concerns about possible side effects to your doctor, your pharmacist or nurse.

Hydroxychloroquine with other medicines

There are some significant potential drug interactions between hydroxychloroquine and some other medications (particularly treatments used for other health conditions) and these risks can be minor or major. It is therefore particularly important that a full and complete medical history is given to the prescribing doctor.

Remember to take care when using any other medications or complementary therapies (even if bought 'over the counter' for colds or flu and, importantly, any antacids for indigestion). Remember to check with a doctor, nurse or pharmacist that they are safe to take with hydroxychloroquine and any other medication taken.

Hydroxychloroquine during pregnancy and breast-feeding

For those who are already taking hydroxychloroquine and wishing to start a family, it is advisable to speak to your consultant about continuing with Hydroxychloroquine.

Hydroxychloroquine must be stopped during the weeks or months of breast-feeding as it is transferred in breast milk.

Hydroxychloroquine and alcohol

As hydroxychloroquine is frequently prescribed alongside other DMARDs it is really important that any advice that relates to another DMARD must be acknowledged and used to guide you when taking Hydroxychloroquine. This is particularly the case when you are taking Hydroxychloroquine with methotrexate and sulfasalazine.

For those over 18 years there is no reason to avoid moderate alcohol consumption whilst on hydroxychloroquine (though advice on alcohol intake will depend on the advice for any other drugs being taken as stated above). Please see our separate articles on other RA medications.
Hydroxychloroquine and immunisation/vaccination

Live vaccines (measles, mumps, rubella (MMR), chickenpox, oral polio (NOT injectable polio), BCG, oral typhoid and yellow fever) cannot be given to anyone already taking hydroxychloroquine. If hydroxychloroquine has not yet been started it is important to seek advice on how long a gap to leave after having a live vaccine.

- The annual flu vaccination and 'pneumovax' protection against pneumonia is permitted
- If possible have 'pneumovax' protection before starting hydroxychloroquine

Flu vaccine is now available in two forms, an injection for adults and a nasal spray for children. The injection is not a live vaccine and therefore suitable for adults taking hydroxychloroquine and is recommended. The nasal spray is a live vaccine and not suitable for adults taking hydroxychloroquine. It is important to discuss having a flu vaccination with your GP.

Hints and tips

Hydroxychloroquine can make skin more sensitive to sunlight. The following tips can help with this:

- Remember to use sunscreen before going into the sun, as well as a t-shirt and hat
- Re-apply sunscreen as frequently as recommended

Vaccination of close family members can help to protect someone with a lowered immune system.
Leflunomide

Leflunomide is a disease modifying anti-rheumatic drug (DMARD) developed specifically to control inflammatory arthritis.

DMARDs act slowly, over weeks and months.

Leflunomide is a prodrug, which means that it is inactive until it is taken. It is changed into the active drug inside the person’s own body.

The overactive immune system in RA causes pain, swelling, heat and redness. Leflunomide dampens down this process by ‘switching off’ the cells responsible for this over-activity. It may also work in several other ways.

Background

Leflunomide has been used as a disease-modifying anti-rheumatic drug to treat rheumatoid arthritis since the early 2000s. Long-term clinical use, during which time it has been given to many people with RA, has shown it continues to be both effective and relatively safe.

Disease modifying drugs are used to treat inflammatory arthritis by decreasing joint inflammation and damage, reducing the risk of disability and enhancing quality of life.

Research into RA has found that the earlier the treatment starts with a DMARD to control the inflammation the better the long-term outcome.

How does it work?

Leflunomide is only prescribed by a specialist experienced in the treatment of rheumatoid arthritis. A detailed medical history is very important to ensure the treatment is suitable for each patient. Blood tests are required beforehand and then usually every two weeks during the first six months of treatment and every eight weeks afterwards.

Leflunomide is prescribed as a tablet of 10mg or 20mg daily dependent on the clinical judgment of the specialist. Leflunomide was previously started with a three-day ‘loading dose’ of 100mg daily, but this has generally been stopped as it led to significant problems with diarrhoea.

Leflunomide acts on an enzyme in the body to limit the excessive reaction of the cells involved during inflammation, thereby reducing the swelling, pain and problems of RA.

Leflunomide persists for a long time in the body so that any change of treatment to a different drug must be carefully managed to avoid the potential that the side effects from both leflunomide and the next drug might cause problems. If necessary, leflunomide remaining in the body can be ‘washed out’ by giving a suitable substance such as activated charcoal over several days.
Most commonly reported side effects

As with any medication, leflunomide has a number of possible side effects, although it is important to remember that these are only potential side effects and may not occur. Side effects may include:

- A rise in blood pressure therefore regular monitoring is advised
- Alteration to some blood test results eg liver tests, full blood count
- Unexplained diarrhoea
- Skin reactions; inflammation of the lining of the mouth
- Increased susceptibility to infections
- Shortness of breath, cough
- Numbness/tingling of feet and/or hands

More information on side effects can be found in the patient information leaflet for leflunomide, which will come with your medicine.

Remember to report any concerns about possible side effects to the doctors, pharmacists or nurses.

Leflunomide with other medicines

- Non-steroidal anti-inflammatory drugs (NSAIDs) and steroid treatment may be continued together with leflunomide
- The efficiency of oral contraceptives is not affected
- Monitoring of warfarin may need to be more frequent
- Caution is needed when leflunomide is prescribed alongside many other prescription medicines

Leflunomide during pregnancy and breast-feeding

Recommendations for women

- Leflunomide is suspected of causing birth defects
- Effective contraception is essential while taking leflunomide and for up to two years after stopping it, or for 11 days using a ‘wash out’ procedure. Blood tests are then required to check the levels of leflunomide and again at 14 days
- Your doctor’s advice is essential on exactly when contraception may be stopped
- Women must not take leflunomide whilst breast-feeding

Recommendations for men

- Leflunomide is suspected of causing birth defects
- For men wanting to father a child reliable contraception is essential for
at least three months after stopping it or for 11 days using a 'wash out' procedure

- Blood tests are then required to check the levels of leflunomide and again at 14 days
- Your doctor’s advice is essential on exactly when contraception may be stopped

**Leflunomide and alcohol**

The recommendation is that alcohol consumption should be avoided during treatment with leflunomide as there is the possibility of increased toxic effects on the liver.

**Leflunomide and immunisations/vaccinations**

There is no research evidence on the effects and safety of vaccinations for anyone taking leflunomide, therefore vaccination is not recommended.
Ciclosporin (Neoral)

Ciclosporin treatment for rheumatoid arthritis is usually an ‘add-on’ treatment to supplement the main disease modifying drug (eg methotrexate) or to enable the reduction of regular steroid treatment.

Ciclosporin is now only used rarely since the continuing development of more effective targeted treatments (see *Biologics and Biosimilars*, P.45)

Ciclosporin is also used to minimise the possibility of rejection of transplanted organs as well as for other inflammatory conditions.

It is accepted practice that ciclosporin is only prescribed by the manufacturer’s trade name of ‘Neoral’ as there are slight variations with the responses seen to the same drug produced by other manufacturers.

**Background**

Ciclosporin was developed in the 1970s and its effects on dampening down the immune system have been used for the treatment of rheumatoid arthritis as well as following kidney and heart transplants.

**Most commonly reported side effects**

As with any medication, ciclosporin has a number of possible side effects, although it is important to remember that these are only potential side effects and they may not occur at all.

Close monitoring with blood tests is important as well as regular blood pressure monitoring and after 6 months of treatment kidney function needs to be checked. When Neoral is prescribed together with another drug that affects the immune system, monitoring will be according to which drug has the most frequently required regimen.

Side effects may include: nausea, vomiting, diarrhoea, swollen gums, raised blood pressure, fever, fatigue, headache and increased risk of infections but this list is not exhaustive.

More information on side effects can be found in the patient information leaflet for ciclosporin that comes with your medicine.

Remember to report any concerns about possible side effects to your doctor, pharmacist or nurse.

**Ciclosporin with other medicines**

There are some significant potential drug interactions between ciclosporin and many other medicines. It is particularly important that a full and complete medical history is given to the prescribing doctor.

Remember to take care when using any other medicines or complementary
therapies (even if bought ‘over the counter’ for colds, flu or other home remedies). **Remember** to check with a doctor, pharmacist or nurse that they are safe to take with ciclosporin as well as with any other medication being taken.

**Ciclosporin during pregnancy and breast-feeding**

Neoral should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the unborn child.

There has been limited experience of pregnant women taking ciclosporin, but the risk of premature delivery has been described.

Ciclosporin passes into breast milk, therefore breast-feeding is not recommended.

**Ciclosporin and immunisations/vaccinations**

Advice about immunisation or vaccination for anyone taking ciclosporin must be obtained from the prescribing specialist consultant.
Azathioprine

Azathioprine is used to control severe active rheumatoid arthritis, usually as an ‘add on’ treatment to supplement the main disease modifying drug (DMARD) or to enable the reduction of regular steroid treatment.

Azathioprine is now only used rarely since the continuing development of more effective targeted treatments (see Biologics and Biosimilars, P.46 and 49)

Azathioprine is also used to minimise the possibility of rejection of transplanted organs as well as for other inflammatory conditions.

Azathioprine damps down the immune system by slowing the rate of cell division amongst the inflammatory cells.

**Background**

Azathioprine has been widely prescribed since the 1960s. The benefit of treatment with azathioprine can take weeks or months to be established.

**Most commonly reported side effects**

As with any medication, azathioprine has a number of possible side effects, although it is important to remember that these are only potential side effects and they may not occur at all.

Close monitoring of weekly blood tests for the first 8 weeks (or as advised) of treatment is very important.

Side effects may include: nausea, vomiting, diarrhoea, throat ulcers, fever, infections, bruising and bleeding but this is not exhaustive.

More information on side effects can be found in the patient information leaflet for azathioprine that comes with your medicine.

Remember to report any concerns about possible side effects to your doctor, pharmacist or nurse.

Azathioprine with other medicines

There are some significant potential drug interactions between azathioprine and many other medicines. It is particularly important that a full and complete medical history is given to the prescribing doctor.

Remember to take care when using any other medicines or complementary therapies (even if ‘bought over the counter’ for colds, flu or other home remedies). Remember to check with a doctor, pharmacist or nurse that they are safe to take with azathioprine as well as with any other medication taken.

Azathioprine during pregnancy and breast-feeding

Azathioprine must not be used during pregnancy without careful assessment of the risks and benefits. Breast-feeding
is definitely not recommended whilst on treatment with azathioprine.

Contraception must be used by both men and women during treatment with azathioprine and for three months after treatment has stopped.

**Azathioprine and immunization/vaccination**

Live vaccines (measles, mumps, rubella (MMR), chickenpox, oral polio (NOT injectable polio), BCG, oral typhoid and yellow fever) cannot be given to anyone already taking azathioprine.

The possible response to killed vaccines (any vaccine that is not ‘Live’) is likely to be diminished because of azathioprine treatment and this results in a reduction of the protection that the vaccination provides.

The annual flu vaccination and ‘pneumovax’ protection against pneumonia is permitted. If possible the ‘pneumovax’ vaccination should be given before starting azathioprine.

**Prescriptions**

Your prescriptions for medication will be free to you if you live in Northern Ireland, Scotland or Wales. In England, however, you may have to pay unless you have an exemption. Any medication that is administered in a hospital, an NHS walk-in centre or by your GP in person (such as injections into a joint) you will not be charged for. But you will have to pay for regular prescriptions unless you are under 16 or over 60, are on one of a number of benefits or have a specific exemption. Your GP or pharmacist will be able to advise you whether you have to pay or not.

If you do have to pay and have to get more than 12 prescribed items in a year, you can save money by getting a Pre-Payment Certificate. They currently cost £104, and you can pay in monthly instalments. Visit [www.nhs.uk](http://www.nhs.uk) or talk to your GP or pharmacist for more information.

You will most likely be in receipt of one or more repeat prescriptions. Talk to your hospital healthcare team and/or your GP practice to find out how the system works in your area. Don’t assume that prescriptions will automatically be renewed.

Your GP practice may also have links with local pharmacies, who will collect the prescriptions for you and make them up.

It’s worth getting to know your pharmacist, whether they are based in your local health centre or hospital or on the high street. Some healthcare teams include a pharmacist with specialist knowledge of RA prescribing (ask your Rheumatology specialist nurse if that’s true in your case). Pharmacists are a valuable source of support and information. He or she can help if you are concerned about your medications or the instructions about your treatment, or if you need to check whether you can take other medications or over-the-counter treatments at the same time.

You can also book an annual ‘Medicines Use Review’ with your pharmacist if, for example, you are taking multiple drugs, including, perhaps, drugs for a condition other than RA.
Our immune system exists to recognise and fight external ‘invaders’, such as viruses, bacteria and other infections. It also plays a role in preventing and destroying tumours. In order to perform these roles effectively, the immune system has developed a complex recognition system to distinguish ‘self’ (the body’s own, healthy tissues) from ‘non-self’ (everything else). The mechanisms underpinning this critical discrimination are collectively called ‘immune tolerance’. Similar mechanisms come into play when there are elements of non-self that it would be dangerous to attack, such as the food that we eat.

As might be expected because of its role, our immune system is everywhere within our body – in our blood, in our lymph nodes and spleen and also in the surfaces that contact the outside world, such as the lungs and the gut. At the microscopic level it consists of various types of white blood cells. These cells are organised into what is essentially an army, with lines of command and regiments of cells, armed with weapons to attack the invader. The weapons include proteins such as antibodies and cytokines. The latter include TNF and IL6.

Given the complexity of the human body, and the myriad of external threats, it is perhaps not surprising that the immune system sometimes makes mistakes (a failure of immune tolerance). Under these circumstances, the attack by one’s immune system is inappropriately directed to a part of self, explaining ‘autoimmune’ diseases such as diabetes, multiple sclerosis and rheumatoid arthritis. In these conditions the full arsenal of the immune system is directed at the pancreas, the central nervous system and joints respectively. Unlike an infection, however, even when a lot of damage has already occurred, the target is not eliminated (unlike a germ) – and therefore these diseases are effectively life-long conditions.

Fortunately, we now know a great deal about our immune system – from the ‘command line’ of cells through to the weapons that cause the damage. Furthermore, with advances in medical technology it has become possible to specifically target and neutralise distinct elements of the autoimmune army. For example, we can neutralise the weapons with drugs that block TNF or IL-6. Or we can target the cells that produce auto-antibodies (B-cells) using rituximab. And we can target the generals of the immune system (T-cells) with abatacept. Each of these strategies has proved to be highly effective in treating patients with RA. Not every drug works for every patient but it is usually possible to find an effective treatment when a patient needs it.

This booklet provides more information on these so-called ‘targeted therapies’ – biologics and biosimilars – in the following pages.
Biologic therapies

Rheumatoid arthritis (RA) is usually treated with one or more of the many disease modifying anti-rheumatic drugs (DMARDs) that are available (as outlined in the foregoing pages). In various ways, these drugs calm down the activity of the immune system so that it stops attacking and damaging the joints.

Conventional DMARDs for RA (such as methotrexate and sulfasalazine) and drugs such as steroids are effective, but they tend to suppress many aspects of the body’s immune response at once. As we have learnt more about the abnormal immune response that happens in RA, it has become possible to develop treatments that target very specific aspects of it: these are biologic therapies.

The NICE RA Guideline states that to be eligible for biologic drugs, patients with RA should have high levels of persistent disease activity. This is measured by a scale known as the Disease Activity Score in 28 joints (DAS 28 for short), which must be 5.1 or higher if you are to be eligible for biologic therapy. (See page ?? for more about DAS28.) You must also have failed on two disease modifying anti-rheumatic drugs (DMARDs), one of which must be methotrexate taken for at least six months unless it is contra-indicated for some reason.

Biologic drugs for the treatment of rheumatoid arthritis (RA) are made from proteins. They work by blocking the activity of a key chemical or cell or protein involved in inflammation that gives rise to joint swelling and other symptoms. They are powerful and specific therapies that target very particular parts of the immune system.

In the 1980s it was discovered that the actively inflamed joints of people with rheumatoid arthritis contain many different chemicals that cause inflammation or contribute to it, produced by cells in the joint. Among these chemicals, proteins called cytokines were discovered, whose job is to send chemical messages from one cell to another. There are many different cytokines: some switch off inflammation while others are particularly potent at causing it.

Biologic drugs are given by subcutaneous injection or some as an infusion into a vein. They cannot be taken by mouth.

NICE and the SMC guide the prescription of biologics and biosimilars and the order in which they are prescribed. However, when moving onto a biologic or biosimilar, for the first time, it’s likely that you will be started on one of the anti-TNFs or a biosimilar anti-TNF (see the tables, right).
### Anti-TNF drugs

<table>
<thead>
<tr>
<th>Generic drug name</th>
<th>Brand name</th>
<th>Target cells of immune system</th>
<th>Dose and method of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>adalimumab</td>
<td>Humira</td>
<td>anti-TNF</td>
<td>40mg by subcutaneous (under the skin) injection every other week</td>
</tr>
<tr>
<td>certolizumab pegol</td>
<td>Cimzia</td>
<td>anti-TNF</td>
<td>400mg by subcutaneous injection at weeks 0, 2 and 4 (given as two injections of 200mg), and then 200mg every other week thereafter</td>
</tr>
<tr>
<td>etanercept</td>
<td>Enbrel</td>
<td>anti-TNF</td>
<td>25mg twice a week, or 50mg weekly by subcutaneous injection</td>
</tr>
<tr>
<td>golimumab</td>
<td>Simponi</td>
<td>anti-TNF</td>
<td>50mg monthly by subcutaneous injection</td>
</tr>
<tr>
<td>infliximab</td>
<td>Remicade</td>
<td>anti-TNF</td>
<td>3mg per kg of body weight by intravenous infusion, repeated 2 weeks and 6 weeks after the first infusion, then every 8 weeks</td>
</tr>
</tbody>
</table>

Possible side effects with anti-TNF treatment: risk of increased infections (sometimes severe), skin reaction to injection site, nausea, abdominal pain, fever, headache and others. Remember to report any side effects to the medical team caring for you.

### Other biologic drugs, targeting different inflammatory chemicals

<table>
<thead>
<tr>
<th>Generic drug name</th>
<th>Brand name</th>
<th>Target cells of immune system</th>
<th>Dose and method of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>tocilizumab</td>
<td>RoActemra</td>
<td>IL-6 (interleukin 6) receptor inhibitor</td>
<td>8mg/kg of body weight as intravenous infusion each month</td>
</tr>
<tr>
<td>rituximab</td>
<td>Mabthera</td>
<td>B-cell depletion of lymphocytes (1 type of white blood cell)</td>
<td>Intravenous infusion twice, two weeks apart, repeated every 6-12 months</td>
</tr>
<tr>
<td>abatacept</td>
<td>Ocrecia</td>
<td>Antibody blocking T-cells</td>
<td>3 x Intravenous infusions every two weeks, thereafter monthly</td>
</tr>
</tbody>
</table>

Possible side effects with other biologic drugs: abdominal pain, diarrhoea, mouth ulcers, altered blood tests, dizziness, hypertension, infections (upper respiratory tract), migraine, flushing, fatigue and others. Remember to report any side effects to the medical team caring for you.

Individual drug information will be given to you at the start of treatment.
What’s in the pipeline?

It is encouraging to know that research and development are continuing year by year and exciting new biologic drugs are already in phase III clinical trials (2016), which means that around 1,000 patients with rheumatoid arthritis, recruited as research participants, are able to add to the knowledge of safety and effectiveness.

<table>
<thead>
<tr>
<th>Generic drug name</th>
<th>Target cells of immune system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarilumab</td>
<td>IL-6 (interleukin 6) receptor inhibitor</td>
</tr>
<tr>
<td>Secukinumab</td>
<td>IL-17 (interleukin 17) receptor inhibitor</td>
</tr>
<tr>
<td>Sirukumab</td>
<td>IL-6 mAb (interleukin 6 mAb) receptor inhibitor</td>
</tr>
</tbody>
</table>

In 2014 it was reported that 92 drugs were in different stages of development for musculoskeletal diseases and conditions. Of these 55 were being developed for the treatment of rheumatoid arthritis. The above table shows 3 of the new biologic drugs targeting IL6 and IL17 which are in advanced stage of trials.

How to report any side effects or adverse reactions to a medicine

If you do experience any side effects or reactions you are concerned about your first port of call should be your rheumatology team or your GP however you can also report directly to the Yellow Card scheme. Medicines and Healthcare Product Regulatory Agency’s (MHRA) which runs the Yellow Card scheme, collates and reviews reports of suspected adverse drugs reactions on all licensed and unlicensed drugs. Since 1964, the Yellow Card scheme has become a cornerstone of the UK’s medicines monitoring system, acting as an early warning for potential side-effects and adverse reactions. yellowcard.mhra.gov.uk

There is even now a Yellow Card app which provides easy reporting of side-effects on the move and brings the scheme into the digital age. You can download the app today from iTunes and the Play Store on your iOS or Android device.
Biosimilars

Biological medicines (biologics) are made from living organisms using biotechnology techniques. Since their introduction at the end of the 90s in the field of rheumatology, biologics have revolutionised the treatment of a number of autoimmune inflammatory diseases and benefited millions of people worldwide.

Many original biologic drugs (called originator drugs) are reaching the end of their patent, meaning other manufacturers are now permitted to produce similar versions of these medicines and these drugs are called ‘biosimilars’. They are not absolutely identical to the original. However, all biosimilar drugs have been required to comply with the rigorous regulation of the original biologics, have shown similar beneficial results, occurrence of side effects and have a comparable record of safety. Data from both groups of drugs are being collected as part of long term research requirements.

Both biologic and biosimilar drugs are prescribed by ‘brand’ name and not by the International Non-proprietary Name (INN- formerly called generic name).

The introduction of biosimilars to world markets has caused considerable disruption to the market pricing of these types of drug because they are considerably less expensive than the originator biologic drugs. This is causing many hospitals to switch people from the original biologics to their biosimilar as originator products come off patent. By doing so, the commissioners, health boards and trusts save money which is significant to them in a cash-strapped NHS. These issues are important and of concern to patients on biologics and to find out more, please visit our website: (www.nras.org.uk/biosimilars)

We anticipate that the transition period of switching patients from originator drugs to the biosimilar as they become available in the UK will extend over a considerable period and we will keep our website up to date as new biosimilars enter the UK market. The process is not simple and to keep up to date with how biosimilars are being used, please refer to our website or call our helpline.

For individual patients the switch from a biologic to a biosimilar drug requires a robust shared decision to be made with the prescribing consultant and the opportunity given to ask and understand the process and what it all means. At present automatic substitution for biologic medicines including biosimilar medicines is not recommended.
<table>
<thead>
<tr>
<th>Brand name</th>
<th>Original Biologic drug</th>
<th>Target cells of immune system</th>
<th>Dose and method of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benepali</td>
<td>Etanercept</td>
<td>anti-TNF</td>
<td>Weekly dose 50mg solution for injection in pre-filled syringe or pen</td>
</tr>
<tr>
<td>Remsima</td>
<td>Infliximab</td>
<td>anti-TNF</td>
<td>Dose 3mg/kg body weight solution for infusion at two, six and thereafter every eight weeks</td>
</tr>
<tr>
<td>Inflectra</td>
<td>Infliximab</td>
<td>anti-TNF</td>
<td>Dose 3mg/kg body weight solution for infusion at two, six and thereafter every eight weeks</td>
</tr>
<tr>
<td>Truxima</td>
<td>Rituximab</td>
<td>B Cells</td>
<td>Intra-venous infusion – dose is exactly the same as for the originator drug Rituximab (Mabthera) which is 1gram at weeks 0 &amp; 2 for the first course of I.V. Further doses at 6-12 months</td>
</tr>
</tbody>
</table>

Remsima and Inflectra are actually both the same biosimilar but just distributed by two different organisations. As further originator biologics come off patent, their biosimilar/s will be allowed to be introduced, once they have successfully passed through the appropriate regulatory process. Many biosimilars are in the pipeline and the above chart represents only those biosimilars available in the UK as at March 2017.
Developing medicines: past, present and future

Professor Peter Taylor, NRAS Chief Medical Advisor, looks at the development of treatments for rheumatoid arthritis, from the early days, when it was first recognised as a medical condition, to the present day. He also mentions potential new treatments with exciting prospects for the future.

The development of effective medication for RA

Rheumatoid arthritis was a very well recognised condition by the early 1900s. In one of the leading textbooks of that time, The Principles and Practice of Medicine by Sir William Osler, it was advised that, “It is useless to saturate the patient with iodide of potassium, salicylates (aspirin) or quinine.” And yet today we still make use of anti-inflammatory drugs, which are related to salicylates, and we also use quinine derivatives such as hydroxychloroquine. The textbook went on to say, “arsenic seems to do good as a general tonic”!

This latter treatment is not a part of contemporary practice, of course. But less than a century after this, and within the last generation, there have been huge advances in science technology that have led to breakthroughs. In particular, improved technology to investigate the physical causes of disease have helped us to identify the key cells and molecules that ‘drive’ chronic inflammation. Secondly, breakthroughs in protein engineering (for which a Nobel Prize was awarded) led to the possibility to selectively inhibit the harmful cells and molecules which had been discovered to cause arthritis. As a consequence of these two advances, the era of so-called biologic disease modifying drugs (drugs made out of proteins from living cells) which are given by injection or infusion came to the clinic in the UK at the turn of the millennium.

Further advances since then have seen new ways of producing biologic drugs and reducing costs of biologic therapies with the introduction of biosimilars. And most recently, advances in chemical engineering have allowed the production of ‘small molecule’ drugs, chemicals which are highly specific for blocking molecules that have been identified within cells that cause chronic inflammation. The advantage of these so-called ‘small-molecular targeted synthetic disease modifying drugs’ is that they can be taken by mouth as tablets, unlike biologic disease modifying drugs.

This extraordinary evolution of effective drug interventions is depicted in the timeline in figure 1, see overleaf.
Therapies for RA have come a long way in the last 100 years.
Innovative new therapies coming to market

'Small molecule cell signalling inhibitors: Jak inhibitors'
Professor Peter Taylor

The biological (Anti-TNF) therapies that came to market at the end of the nineties and those targeting other parts of the immune system, such as IL6, B Cell and T Cell blockers, introduced in the early 2000s, are all large-molecule biologic therapies which work by blocking action on the outside of cells. Because they are very large molecules they cannot be taken orally and are injected subcutaneously (under the skin) or given by intravenous infusion (or 'drip').

JAK inhibitors are new small-molecule therapies that work on the inside of cells to affect cell signalling. Two of these new drugs are coming to the UK market in 2017. Because they are small molecules, they can be taken by mouth and herald a new class of so-called 'targeted synthetic' disease modifying drugs or 'small molecules' because unlike biologic drugs that are made in living cells and comprise large numbers of atoms, the 'small molecules' are chemicals comprising just a relatively few atoms.

What does cell signalling mean? Cell signalling has to do with the way that cells communicate with one another. The tissues and organs of our bodies are comprised of different sorts of cells and the material they secrete around themselves. In order for the organs and the whole body to function as a coordinated and integrated whole, the cells need to communicate with each other. One family of molecules that communicate between cells in this way are known as "cytokines". Cytokines are small proteins that take part in all biological processes involved in health such as growth and repair, movement of cells, manufacture of blood and the regulation of immune function that in health protects us. But cytokines are also involved in the regulation of inflammation. In diseases, such as rheumatoid arthritis, these inflammatory cytokines are over active and fail to 'switch off' immune responses.

A very important group of new drugs that have shown very impressive efficacy with an acceptable safety profile are the Jak inhibitors. "Jak" is an acronym for the scientific term for a particular category of signalling molecules within the cell (Janus kinases). Two such drugs have undergone very extensive clinical trials and have approval for use in some parts of the world. Two Jak inhibitors that are expected to become available in the UK in 2017 are tofacitinib (trade name Xeljanz) and baricitinib (trade name Olumiant). These are oral drugs. They have a similar magnitude of benefit to biologic anti-TNFs.

There are other Jak inhibitors in clinical trials at an earlier stage of development.
Comments
from Reader Reviewers of this booklet, all people living with RA

“Overall, I would say the booklet definitely achieves the aims that are set out on page 5. Since my diagnosis, I’ve not come across any literature that lists the medicines and info about them in this way, and it has helped me to gain a bit more context of where my treatment sits within the whole spectrum of treatments available. I hope you don’t mind, but I’ve copied and pasted a bit of it to show my parents because for parents/relatives of someone with RA, it’s a really clear, informative booklet. And it’s not scary to read either. I feel that as an information provider, the booklet is excellent.”

Ellie, aged 33, diagnosed 2 years ago

“I think this is a great booklet that will be an essential guide for people with RA and their families/carers.”

Jenni, aged 55, lived with RA for 7 years

“Overall I think this will be a great booklet/reference for people with RA.”

Richard, aged 48, lived with RA for 2 years

“I really feel that it is crucial for RA patients to fully understand the disease, the symptoms and the options of treatments available. Therefore, enabling them to accept the condition and learn how to live with it. This booklet explains it all in an easy to read format with clear headings without it being a scary read! So overall a very useful and informative booklet. Yet again, well done NRAS :}“

Donna, aged 42, lived with RA for 21 years
And finally...

We hope that you will have found this booklet useful in informing you about the large range of medications that may be used in the treatment of rheumatoid arthritis and that it will help you to get the best results from your treatment as you engage with your rheumatology team. We also hope that in reading this booklet that you will have noticed the huge advances in medical science that have taken place over the last 25 years and revolutionised the achievable outcomes for people with rheumatoid arthritis.

The outlook for people with rheumatoid arthritis is better than ever before and further treatment advances are anticipated. And remember that NRAS is here to provide you with help and support so that life can be lived to the full!
## Glossary

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adherence</strong></td>
<td>Taking your medication at the times and in the doses prescribed by your doctor</td>
</tr>
<tr>
<td><strong>Advocacy</strong></td>
<td>Support and encouragement given by one person, on behalf of, and, for the benefit of, another</td>
</tr>
<tr>
<td><strong>Alternative therapy</strong></td>
<td>Also known as ‘complementary therapy’. Refers to treatments used in addition to or as an alternative to those prescribed by your doctor. Examples would include acupuncture or homeopathy. There is no evidence that these treatments can control your disease and it is strongly recommended that you tell your health team if you plan to try any of them.</td>
</tr>
<tr>
<td><strong>Blood chemistry</strong></td>
<td>The chemical make-up of the blood which can be analysed by various blood tests, such as glucose, iron or protein tests</td>
</tr>
<tr>
<td><strong>Composite</strong></td>
<td>Made up of several parts or elements</td>
</tr>
<tr>
<td><strong>Concomitant</strong></td>
<td>Having another condition alongside your RA or taking different medications at the same time</td>
</tr>
<tr>
<td><strong>CRP</strong></td>
<td>C-reactive protein is produced by the liver and can be measured in the blood as a marker for inflammation</td>
</tr>
<tr>
<td><strong>Disease activity score</strong></td>
<td>DAS 28 - The combination score of a patient’s specific 28 joints for swelling and tenderness, a recent blood test for inflammation and both the patient’s and the doctor’s assessment of how the disease has been over the previous 7 days</td>
</tr>
<tr>
<td><strong>Equitable</strong></td>
<td>Reasonable and fair</td>
</tr>
<tr>
<td><strong>Escalation</strong></td>
<td>In medical terms, a ‘ramping up’ of the condition or the treatment</td>
</tr>
<tr>
<td><strong>ESR</strong></td>
<td>Erythrocyte (red blood cells) sedimentation rate is a measurement of inflammation in the blood</td>
</tr>
<tr>
<td><strong>Holistic</strong></td>
<td>Having regard to the ‘whole’ needs of a person; the physical, mental, social and spiritual aspects of a person’s life</td>
</tr>
<tr>
<td><strong>Inflammation</strong></td>
<td>Is a normal protective mechanism of our bodies but in RA, the body’s immune system mistakenly attacks the lining of the joints, causing swelling, pain, redness and heat, which are the classic signs of inflammation</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>-----------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Molecule</td>
<td>A group of atoms bonded together, representing the smallest fundamental unit of a chemical compound that can take part in a chemical reaction</td>
</tr>
<tr>
<td>Phase III trial</td>
<td>All new drugs have to go through several stages of testing for safety and efficacy. Drugs that pass a phase III trial, which is a large trial with many participants that focuses on the effectiveness of the drug, will generally go on to be licensed for prescription by doctors</td>
</tr>
<tr>
<td>Remission</td>
<td>To be symptom-free</td>
</tr>
<tr>
<td>Tight control</td>
<td>A plan for treating RA to keep disease activity at the lowest level possible by close monitoring and early treatment of symptoms</td>
</tr>
</tbody>
</table>
Join us

You can become a Member of NRAS for as little as £20 a year.*

You will be helping our work and helping us to provide help and support to all affected by RA. In addition, you will become part of a vibrant and supportive community of people affected by RA. You will also receive a variety of Member benefits, including:

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- monthly email updates
- an invitation to attend our FREE meetings and events
- and more

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*if you pay by direct debit.
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Three further key publications launching in 2017

New2RA

*New2RA* is for people who are newly or relatively newly diagnosed and contains the information you need to help you make sense of and understand what RA is and what you have been told by your rheumatology team. In the early stages of coming to terms with your diagnosis, there are lots of things you don’t know and may want to ask questions about. This booklet will answer those questions and sign-post you to other reliable sources of help.

Living Better with RA

*Living Better with RA* is for people with established disease who have some knowledge of their disease and treatments but want to know more and how to manage their RA as well as possible to get the best out of life. It includes information about other conditions which people with RA are at greater risk of getting, such as heart disease and addresses the importance of developing good self-management and health behaviours to maximise quality of life.

Coping with Fatigue

*Coping with Fatigue* is an important topic for most people living with RA. It ranks alongside pain as one of the most debilitating symptoms of RA. There are lots of things that you can do to help reduce and sometimes prevent fatigue from being overwhelming and this booklet aims to equip you with the knowledge and resources to reduce its impact on your daily life.