EYE WITNESS REPORT

BIOLOGICS IN RHEUMATOID ARTHRITIS

By Nigel Hawkes
ABOUT THE AUTHOR

This report has been authored by Nigel Hawkes, independent science and health journalist. Nigel graduated from Oxford with a degree in metallurgy in 1966, and has written about science, health and international affairs in a career that began on the staff of Nature and included long spells at The Observer (1972-90) and The Times (1990-2008). He retired from The Times in 2008 after eight years as Health Editor, and is now a columnist and regular contributor to the British Medical Journal. Between 2009 and 2012 he was Director of Straight Statistics, a pressure group set up to campaign for the honest presentation and use of statistical data by government, media, and others.

He has written a number of books, including “Structures”, a book about building and civil engineering, and more than 40 science and technology titles for children and teenagers. He was awarded the British Nutrition Foundation Prize in 1992, appointed CBE in 1998 for services to the newspaper industry and science, and was the Medical Journalists Association health writer of the year in 2007 and freelance writer of the year in 2011.

The Eye Witness report has been commissioned and funded by Pfizer. Health journalist Nigel Hawkes developed the report based on insights from patients, public figures and leading rheumatology professionals who have been affected by the evolution of rheumatoid arthritis (RA) treatment and Pfizer’s input has solely been to approve the final report in line with the ABPI Code of Practice.
For many years, rheumatoid arthritis was a disease in the shadows. Doctors did not understand its causes and lacked the means to treat it effectively, many wrongly believing that with bed rest and painkillers the majority of patients got better. The public saw it as a disability of the old with vague and sometimes disbelieved symptoms, while a lot of patients persuaded themselves it was a consequence of age which they must bear with as much stoicism as other aches and pains. Many spent their lives out of sight, unable to work and trapped in their homes, with occasional respite visits to hospital. “There was no talk about remission, or even getting your disease under control” says Ailsa Bosworth, founder of the National Rheumatoid Arthritis Society, who was diagnosed with RA in her early 30s. “It was very much about ‘yes, how can we relieve your pain?’”

Since RA was first given a name in the mid-19th century, many theories about its origins have been advanced, some favouring an infectious cause, others believing there to be a genetic link. Today it is known that the symptoms of RA are caused by friendly fire, when the body’s immune system turns its energies into attacking itself - it belongs to the class known as auto-immune diseases. What triggers this misdirected attack remains unknown, but it could be an infection, an injury, stress, a genetic predisposition, or other factors yet to be discovered.

The immune system is complex and exquisitely specific. Normally it is marshalled into action by the presence of an invader, such as a virus, a bacterium, or a tumour. It recognises the invader as foreign, and attacks it using weapons designed to defeat the invasion without damaging anything else, desisting as soon as the battle is won. To pull this off, it has to distinguish between “self” and “non-self”, between its own tissues and those of the invader. In RA and other auto-immune diseases something goes wrong. The tissue of the joints is mistakenly seen as “non-self” and a concentrated attack is launched. And because the joint tissue never goes away, the attack continues: acute inflammation becomes chronic, damage multiplies (including pain and swelling), and the joints are eroded.

RA is not a rare condition. There are 690,000 affected people in the UK and 26,000 new diagnoses every year, which makes it commoner than multiple sclerosis or leukaemia. Nor is it restricted to older people; 12,000 children under 16 suffer the juvenile form of the disease. Although the joints are the principal focus, RA can affect many other organs as well. There is considerable variation in the symptoms. Professor Ali Jawad, Consultant Rheumatologist at the Royal London Hospital says: “Two thirds of patients present with arthritis affecting mainly the small joints of the fingers on both hands. Quite often the wrists are affected and the knees, the feet to a lesser extent. Then in decreasing order it would be the elbows and the shoulders and the hips.”

The effects can be crippling, both physically and psychologically. When Mary Cowern was diagnosed with RA at the age of 20, her first reaction was disbelief. “I think my first words were ‘You must have got that wrong – I can’t have rheumatoid arthritis, I’m too young.” But disbelief quickly turned into despair as her symptoms worsened and her work as a shop manager became more and more difficult for her. “I was worried about how my life would pan out” she says. “I could see myself becoming more disabled and then wondering where this would end. I was only in my 20’s and my life seemed to be quite over.”

The data show her fears were not exaggerated. The National Audit Office (NAO) found in a report published in 2009 that people with RA take 40 days sick leave a year, compared with the national average of 6.5 days. A third have been forced to give up work within two years, and half within ten years. Since three quarters of those diagnosed with RA are of working age, the impact on the benefits system and the economy as a whole is substantial. While the NAO found that healthcare costs for treating RA are large, at £560 million a year, they are dwarfed by the costs in sick leave and disability payments of £1.8 billion. The NAO does not attempt to estimate the cost to the economy of the lost productivity of RA patients but the NRAS puts it at £8 billion a year.
In the middle of the Ashdown Forest in Sussex, a leading centre for hip and knee replacement surgery operates with great success far from the great centres of medicine – quite a long way, indeed, from any other hospital. The Horder Centre is remote because it started its life as a place where patients with RA, with no cure in sight and not much to alleviate their pain, could find peaceful respite among the trees. Inspired by its founder Cecilia Bochenek, who had contracted juvenile RA at the age of six, the centre was opened in 1966 by Princess Margaret. Without stretching a point, it offered hospice care to the living at a time when medicine could offer little more.

Many patients then spent part or all of their time in hospital. The 1993 edition of the Primer on Rheumatic Diseases, the leading professional title on the subject, said that the foundation of treatment was rest combined with Diseases, the leading professional title on the subject, said time when medicine could offer little more. that the side-effects were severe and in some cases fatal. Steroids provided no permanent answer, but continue to have a role in damping down flares. Gold-based medicines and penicillamine were more encouraging, the first to have an effect on the progress of the disease rather than merely its symptoms. “Some of the happiest patients are the ones that respond really well to gold” says Dr Walker. Sulfasalazine, one of the anti-bacterial sulfa drugs, had been tried in the 1950s because of suspicions that RA might be caused by an infection, and it proved moderately effective. Hydroxychloroquine, an anti-malarial drug, was found to have immune-suppressing qualities and joined the armoury. Most importantly, a cancer drug, methotrexate, was found to work surprisingly well. This group of disease modifying anti-rheumatic drugs (DMARDs) formed the basis of treatment in the pre-biologic era. (It was the success of these drugs that caused the Horder Centre to switch from RA to hip and knee implant surgery for osteoarthritis.)

The use of steroids such as cortisone to reduce inflammation and suppress the immune response had been hailed as a huge advance, but experience showed that the side-effects were severe and in some cases fatal. Steroids provided no permanent answer, but continue to have a role in damping down flares. Gold-based medicines and penicillamine were more encouraging, the first to have an effect on the progress of the disease rather than merely its symptoms. “Some of the happiest patients are the ones that respond really well to gold” says Dr Walker. Sulfasalazine, one of the anti-bacterial sulfa drugs, had been tried in the 1950s because of suspicions that RA might be caused by an infection, and it proved moderately effective. Hydroxychloroquine, an anti-malarial drug, was found to have immune-suppressing qualities and joined the armoury. Most importantly, a cancer drug, methotrexate, was found to work surprisingly well. This group of disease modifying anti-rheumatic drugs (DMARDs) formed the basis of treatment in the pre-biologic era. (It was the success of these drugs that caused the Horder Centre to switch from RA to hip and knee implant surgery for osteoarthritis.)

They waited until you were disabled before they gave you anything faintly useful

But the prospects for many patients remained poor. “We used to wait until patients had bone erosions on their X-rays before we would intervene with the odd DMARD that we had, so it was late and inadequate treatment with potentially toxic and not very effective drugs” Dr Walker says. “Methotrexate came along in the early 1990s. It was an old-fashioned cancer drug but the dermatologists had been using it for psoriasis, and they used to do liver biopsies every two years in case it was damaging the liver. We were very anxious about using it because of that, because a liver biopsy has a mortality attached to it.”

Caution was the watchword. The pyramidal approach meant starting slowly, one drug at a time, then trying another if that failed, and slowly building up to the more potent but potentially more toxic drugs such as methotrexate. Dr Louise Warburton, a GP with a special interest in rheumatology, recalls her first job at the Robert Jones and Agnes Hunt Hospital in Oswestry, in 1992. “We just had the basic DMARDs – I don’t even think we used methotrexate then, because it wasn’t around, so we used sulfasalazine as one of them, and hydroxychloroquine, and there was something called penicillamine. They were fairly basic drugs. They are not very effective in aggressive disease and they have lots of horrible side effects, really. When I first started that job, it was a shock to the system to say the least because there were people with extremely advanced joint disease that wasn’t being properly controlled. They were awfully disabled – they came in wheelchairs, or with walking sticks or Zimmer frames. It was a huge, massive problem for them all.”

Alison Kent, a rheumatology nurse specialist at Salisbury NHS Foundation Trust, began work at about the same time as Dr Warburton. “The treatment goals were about trying to keep patients’ disease as quiet as you possibly could, and keep them pain-free. The treatment pyramid was to start slowly and build up, so as your disease progressed you received higher treatment. I would spend a lot of time doing counselling and education and supporting, because it was helping people to live with the condition. We hardly ever used the word ‘remission’ at all.”

Pamela Adams, an RA patient from Worcester, was diagnosed with the disease more than 30 years ago, when she was 29. She had never heard of RA: “My understanding was old people got it. I was 16 at the time and I had noticed that my knees were very painful. We used to call it my arthritis. We used to say that we had arthritis. We never said it was rheumatoid arthritis.”

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“*And it didn’t just affect your joints, it affected everything*”

Professor Jawad carried out an audit of the time RA inpatients spent at the Royal London in 1999, and discovered it took 6,000 bed days – equivalent to 240 patients each spending an average of ten days in the hospital during the course of the year 40. At that time, the London employed four surgeons who operated on the hands of the RA patients – two orthopaedic surgeons and two plastic surgeons. Professor Peter Kay, consultant orthopaedic surgeon at Wrightington Hospital near Wigan, who is National Clinical Director for Musculoskeletal Services, says that it used to be commonplace to see people with RA who were really quite crippled, with deformities – twisted hands and fingers, and in wheelchairs. “We still do joint replacements in RA patients, but it is less common than it used to be,” he says. “The really bad deformities that you used to get, particularly affecting the hands and upper limbs, that was a major problem but you see an awful lot less of that.”
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The key ingredients of most drugs are chemicals in the form of small molecules able to penetrate almost any part of the body through the bloodstream. They work by interfering with the activity of the protein molecules, a thousand times larger, that make up the organs. But this is not how the body's own defences work; the immune system does not generate tiny active substances akin to drugs, but instead mobilises large proteins called antibodies to attack invaders. These are tailored to the precise job they have to do, and switched off when that job is done. Matching this precise and specific mode of action has long been a dream of drug developers.

The first sign that it might be possible came in 1975, when César Milstein and Georges Köhler at the Medical Research Council's Molecular Biology Laboratory in Cambridge devised a way of creating an endless supply of antibodies in a test tube. Building on the work of many previous researchers, they did this by taking immune system cells from the spleen of a mouse that had been challenged by a foreign protein (sheep red blood cells) to stimulate the production of antibodies. The problem that had stumped earlier researchers was that such cells, grown outside the mouse in a culture medium, do not continue producing antibodies for very long.

Milstein and Köhler had the bright idea of immortalising the immune system cells by fusing them to mouse tumour cells. Tumours do not die off as normal cells do, but continue proliferating indefinitely. The two scientists hoped this fused hybrid cell would produce an single antibody against the foreign protein. To their joy, they were right. They called the product a hybridoma, because it was a hybrid that owed half its parentage to a cancer, a teratoma. Later, because the product of such cells is a single line of identical antibodies, they became known as monoclonal antibodies.

Their advantage was that they could be produced in vast quantities, to target almost any antigen. Their disadvantage was that they were based on mouse, not human, cells, and would be recognised as foreign by any patient into whom they were injected and attacked by the patient's own immune system. Producing human monoclonal antibodies proved difficult, but there were ways to "humanise" mouse monoclonal antibodies, also pursued at Cambridge, using recombinant DNA methods.

While Milstein (who shared the 1984 Nobel Prize for Medicine with Köhler and a third scientist, Niels Jerne, for the discovery) did not at first realise the economic potential, it has proved enormous: the market for monoclonal antibody drugs now exceeds $50 billion a year.

The potential for monoclonal antibody medicines in RA emerged with the discovery that a naturally-occurring protein, tumour necrosis factor (TNF) is a major regulator of the inflammation process. TNF (which acquired its misleading name from experiments showing it could destroy tumour cells in test tubes) is a cytokine, a class of small proteins that act as messengers. Of these, a form of TNF called TNF alpha is the most important in RA, acting as a ringleader encouraging other cytokines such as interleukin-1 (IL-1) and interleukin-6 (IL-6) to produce the enzymes that actually destroy cartilage and bone. In 1983 a study at the Kennedy Institute at Hammersmith Hospital in London demonstrated that a monoclonal antibody drug targeted at TNF alpha produced a marked reduction in inflammation (9). The drug was infliximab, developed in the US.

Bioscience reached the clinic in the late 1990s, producing compelling results in many patients. Mary Cowern had her first injection on a Tuesday. She had read about the new drugs and admits it was quite a scary moment for her. Not only was she terrified of needles, but she worried that this was her last chance and that it might not work. The effect was swift, and took her by surprise. "A couple of days later I had got up, gone downstairs and was making a cup of tea, and I suddenly thought 'Oh my God, that was so easy'. It literally was that instantaneous for me. Whereas normally I would struggle out of bed, I would shuffle downstairs, I would struggle to fill the kettle. It was so much easier and I was thinking this must be in my head. I rang my Rheumatology Team and spoke to the nurse there and she said: 'You aren't the first patient to say this'.

Not everybody reacted so swiftly or so well, but the clinical results show that biologics plus methotrexate work much better than methotrexate alone. “You get this much benefit from methotrexate” says Dr Walker with his fingers close together, “you get this much benefit from biologics” - widening the spacing - “and if you take the two together you get this much benefit" opening his hands wide.

His experience is that roughly 80% of patients respond in a worthwhile way. This is measured by a system devised by the American College of Rheumatology, which comprises three categories, ACR20, ACR50 and ACR70, the numbers referring to the percentage improvement in symptoms. “It’s roughly how much better they are, so an ACR70 means that the patient is 70% better. Nearly all the figures with all the biologics are that 60% get an ACR20, 40% an ACR50, and 20% an ACR70.”

The impact on the benefits system and the economy as a whole is substantial.
Trial results of five biologics (infliximab, etanercept, adalimumab, golimumab and certolizumab) confirm his view that all fall within a similar range of effectiveness. Benefits have included far fewer inpatient stays. At the Royal London they fell from 2,400 bed days in 1999 to just 180 in 2006, after biologics became established 16. “That is a dramatic impact” says Professor Jawad. The number of surgeons who operate on damaged joints at the hospital has fallen from four to one. “Really you could say we have shifted the expectations” he says. “Now we are achieving remission in RA, we are preventing an accumulation of damage and we are preserving quality of life.”

A diagnosis of RA has in the past generally led sooner or later to leaving the job market. But many patients on biologics can continue in work, or return to it like Mary Cowern. She now works as the Welsh Director of the charity Arthritis Care. “I am back working full time which I never thought I would be able to do ten years ago. I am in a relationship and I have a step-daughter so I have family life. All the things I thought had been taken away from me, I got back. It might sound a bit corny but I have got the old me back, because I am a lot more positive. It is really phenomenal for me the difference it has made.”

“My job has changed dramatically because we are now talking to patients about remission, and keeping them in work”

Success in so many cases means that RA, once invisible because it drove people from sight, is now invisible because it is so much better treated. That’s a slight worry for Professor Peter Kay, who as National Clinical Director for Musculoskeletal Services is anxious to ensure the specialty has a visible profile. “The trouble with musculoskeletal stuff is that it is not quite as emotive as kids, cardiac and cancer” he says. “It doesn’t hit the specialty has a visible profile. “The trouble with musculoskeletal stuff is that it is not quite as emotive as kids, cardiac and cancer” he says. “It doesn’t hit the same priority.”

That is important because despite the great success of RA treatment in the biologic era, not every single patient benefits. There are some for whom biologics work less well, not at all, or diminish in effectiveness over time. There are also fears over the ability of the NHS to exploit the “window of opportunity” to stop RA in its tracks by prompt diagnosis, referral and treatment.

While the NAO found that healthcare costs for treating RA are large, at £560 million a year, they are dwarfed by the costs in sick leave and disability payments of £1.8 billion. The NAO does not attempt to estimate the cost to the economy of the lost productivity of RA patients but the NRAS puts it at £8 billion a year.
If having these drugs enables somebody to go back to work and start paying tax instead of claiming benefits, that has a direct impact on the wider society and on government.

If patients do not respond to conventional DMARDs within six months, and their DAS28 score is greater than 5.1 on at least two occasions one month apart, they may then be prescribed biologics, normally in combination with methotrexate. Biologic treatment should only be maintained if there is an improvement of at least 1.2 in the DAS28 score at six months, and if it is sustained at subsequent six-monthly appointments. If the first biologic fails, patients may move on to rituximab plus methotrexate, which should also be subject to the same six-monthly checks.

Ailsa Bosworth of NRAS does not believe that this guidance ensures that all patients who should be on biologics actually are. She argues that the threshold is too high and the sequencing has more to do with the order in which the drugs were introduced than it does to their clinical benefits. “The threshold was cautiously set, quite rightly at the time, because we didn’t know what the long-term outcomes would be, and we were concerned about greater cancer risk, so it was right to be cautious. But there are quite a large number of people who fall into the 3.6 to 5.1 DAS score who will do as badly as people with a DAS score of greater than 5.1. So I think we are not doing enough.” The British Society for Rheumatology agrees, arguing that the threshold should be reduced to a DAS score of 3.2 together with at least three or more tender and three or more swollen joints.

A comparison of the variations in guidelines in use across Europe, funded by Merck Sharp and Dohme, found little consistency in the 12 countries studied. “The potential to tackle RA and limit the burden of disease is now well-established, but the will to do so in some countries appears to be weak”, the report concluded. “Of the 12 countries studied this lack of will is most evident in England, where access to modern biologic therapies is heavily restricted until a patient’s burden of disease has become severe. Compared to other European countries this seems to be too little, too late.”

These findings were supported by a 2010 report by Professor Sir Mike Richards, the former National Director for Cancer, and now Chief Inspector of Hospitals. Charged by the Health Secretary with investigating the international variation in the use of drugs in 14 countries, he concluded that the UK came tenth out of 14 in its use of RA drugs – two places worse than in its overall ranking, which was eighth.

The UK approach to biologics has found a doughty opponent in Sal Brinton, Liberal Democrat health spokesperson in the House of Lords, who suffers from RA. Baroness Brinton has found accessing biologics difficult and their effect limited. Diagnosed eight years ago, she is one of the unlucky ones who do not respond well, and she is now in a wheelchair. Her blood tests were negative – “therefore I don’t get an automatic route to biologics until I am in a wheelchair. Her blood tests were negative – “therefore I don’t get an automatic route to biologics until I am in a wheelchair.”

It took quite a while even to get on to methotrexate. I also had ten DMARDs before moving on to biologics.”

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The rigid interpretation by her Clinical Commissioning Group (CCG) of the NICE guideline forced her to take rituximab with methotrexate when she failed on her first biologic, against her wishes and those of her consultant because it was contraindicated. “The CCG insisted that the pathway be followed, even though NICE says that you must also look at the patient’s response”, she says. “I am not alone. I am on the RA bulletin boards, on Facebook, on NRAS; it is a repeated problem.”

Like others, she is critical of delays in referral. “Some GPs (but not mine!) are woefully ignorant - the problem is that they receive very little musculoskeletal and auto immune disease training. This needs to be remedied.” It is a criticism echoed by Dr Warburton: “GP training schemes don’t spend much time on RA, and the problem is that GPs will probably only see one case every two years of new rheumatoid in their surgery. The obvious cases are obvious, but even some of those are not referred promptly”. Ailsa Bosworth believes that occasions where patients are being referred as rapidly as the guidelines suggest are “very rare”, despite evidence that if you can treat somebody within that 12-week window of opportunity you have a much better chance of getting them into remission. The NAO report found that people with RA visit a GP four times on average before being referred – and 18% of them visit eight times before a referral.

Peter Kay, with overall responsibility for musculoskeletal conditions for NHS England, says: “These are expensive drugs but the response is quite impressive. Obviously if you consider the societal costs, they are not as expensive as they seem. I regard it as being really important that people present early, are diagnosed early, and receive treatment early.”

The danger, as Ailsa Bosworth sees it, is that NICE’s remit is drawn so narrowly that it leaves too much out of consideration. “NICE has done a lot of good, but is only looking at half the picture. If having these drugs enables somebody to go back to work and start paying tax instead of claiming benefits, that has a direct impact on the wider society and on government. Not to take that into account when you are evaluating the health economic benefit of these drugs is completely illogical and misleading.”
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5. Personal communication, unpublished data
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