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Review Article

Rheumatoid Arthritis Treatments: A Historical Perspective

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Submitted: 07 July 2016

Accepted: 25 July 2016

Published: 28 July 2016

Keywords

- Rheumatoid arthritis
- Treatments
- History of medicine
- DMARDs
- Biologics

Abstract

The diverse selection of treatments for Rheumatoid Arthritis (RA) have had a complex evolution. Observational studies demonstrated the benefit of Non-Steroidal Anti Inflammatory agents and conventional synthetic disease modifying agents (DMARDs). Of the DMARDs, Gold and Sulfasalazine were employed in the assumption they were treating arthritis with an infectious aetiology. Glucocorticoids promised to be the cure they did not provide, initially side-lined due to their adverse effects. The conventional DMARD, Methotrexate remains the anchor drug to induce and maintain remission.

The array of medications in use has widened with our deeper understanding of the complex pathogenic processes underlying RA. Treatments originally designed to treat sepsis resulted in the conception and use of targeted monoclonal antibodies (biologics). The demonstration of cytokine mediated autoimmunity present in RA has more recently led to the oral targeted synthetic alternatives, including the Janus Kinase (JAK) inhibitors. These medications do not come without a significant monetary and side effect cost.

As we observe the mechanisms of drug development revolutionize, with safer mechanisms of drug delivery and the informative role of genomics, we can hope for less harmful and more efficacious targeted therapies for this chronic debilitating condition. Paying attention to the historical ways in which we have developed our drug formulary allows us to reflect upon and foster those techniques for the aim to reduce disease progression, strive for longer remission and possibly curative treatment.

ABBREVIATIONS

RA: Rheumatoid Arthritis; DMARD: Disease Modifying Anti-Rheumatic Drug; MHC: Major Histocompatibility Complex; ACPA: Anti-Citrullinated Peptide Antibodies; RF: Rheumatoid Factor; NSAID: Non-Steroidal Anti-Inflammatory Drug; JAK: Janus Kinase; Jakinibs: Janus Kinase Inhibitor; COX: Cyclo-oxygenase; IL: Interleukin; MMP: Matrix Metalloproteinase; MAP: Mitogen Activated Protein; SSZ: Sulfazalazine; TNF: Tumour Necrosis Factor; EULAR: European League Against Rheumatism; mAB: Monoclonal Antibody; FDA: Food and Drug Administration; IL-1R: Interleukin 1 Receptor; IL-6R: Interleukin 6 Receptor; CTLA: Cytotoxic T-Lymphocyte-Associated Protein; EMA: European Medical Agency

INTRODUCTION

Rheumatoid arthritis (RA) has been a historically difficult to treat condition; in 1976, F Dudley Hart said of RA *'the treatment of a condition for which there is no positive cure makes much greater demands on the doctor, who has to be a practical pharmacologist, human being, psychiatrist, and father confessor- he has, in fact, to be a proper physician in the fullest sense of the word'* [1]. Though RA is still not curable, as we have developed our understanding of the condition, the armoury of medications employed to arrest its progression has vastly increased and long-term remission is a reality for most patients.

Rheumatoid arthritis is an inflammatory arthropathy with multi-organ involvement. Relatively common, it effects between 0.5 and 1% of the population [2], with evidence of increasing prevalence correlating with increasing latitude and when comparing rural to urban populations [3]. The arthritis that ensues is destructive and typically symmetrical, affecting predominantly small joints. A debilitating disease, it carries a vast cost to individual and society. The patient suffers from a disabling arthopathy, increased prevalence of co-morbid conditions such as atherosclerotic disease, as well as reduced participation in society and resultant impact on quality of life [4]. Indirect cost to

society, such as reduced work capacity has been estimated to be as high as €45.3 billion in Europe and €41.6 billion in the United States [5]. Accordingly treatment strategies for RA have been long sought after, with the disease course now a lot more favourable as a result.

Historically, therapies for RA were trialled on the notion the disease was infection driven. This led to the use of gold and sulpha containing remedies, with limited success. Observational studies helped discover 'blockbuster' medications such as steroids, widely viewed as a 'cure', early in its use [6]. Consequently, the success of various therapeutic agents has helped inform the scientific community of potential pathogenic mechanisms in RA. As our understanding of the disease has improved, we have moved on to more targeted therapies. Today, our focus has gone beyond disease course modification to tailoring therapy to individual patients, taking into consideration treatment effect, tolerance and convenience for the patient.

The aetiology of RA is thought to be dependent on both environmental and genetic factors. Of these, the major modifiable environmental risk factor identified is that of smoking [7]. Heritability of this condition has been reported as high as 65%, with various polymorphisms identified on genome wide studies, along with identification of susceptibility Major Histocompatibility Complex MHC genes including the HLA-DRB1 allele. It is noted that disease associated alleles demonstrate common amino acid sequences in the peptide binding groove, fuelling an antigen driven pathogenic mechanism. Further, well characterised autoantibodies such as Rheumatoid factor and anti-citrullinated peptide antibodies show a strong association with the presence of the shared epitope [4].

The early identification of circulating immune complexes in RA encouraged the use of plasma exchange as a modality of treatment with the belief they were pathogenic; the results, however, were not convincing [8]. A current proposed mechanism is of citrullinated antigen binding by Anti-citrullinated peptide antibodies (ACPAs), with subsequent binding by RF and the formation of immune complexes and activation of inflammatory cascades. Interestingly, ACPAs can be identified well before the clinically apparent phase of RA, with a progressive rise in inflammatory cytokines leading up to organ involvement. Though we rarely demonstrate evidence of ACPA seronegativity, circulating concentrations of both RF and ACPA are seen to decrease with current treatment methods [4].

Therapies currently employed to combat RA include traditional treatments such as glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs), and disease-modifying antirheumatic drugs (DMARDs), classified broadly as synthetic (encompassing the traditional DMARDs and newer therapies such as JAK-2 inhibitors) and biological drugs. The broad aim is to suppress the culpable immune system, but this is consequently accompanied by an increase in the risk of infections suffered by the host.

Historical methods for treatment (early concepts)

Just over a hundred years ago Bain and Edgecombe referred to arthritis deformans (or rheumatoid arthritis) and advocated adequate nutrition, treatment of the indigestion and Spa therapy as the treatments of choice [9]. Only 30 years later, Price's Textbook of the Practice of Medicine (1934) describes RA as either primary or secondary to infection. At this point the main stay of treatment was to eradicate the "infective foci." This idea also supported the view that vaccinations were beneficial, along with iodine and iodides and intestinal antiseptics [1].

F Dudley Hart gives an alphabetized list of common treatments (Figure 1) in use at the time of writing in 1976, highlighting the poor understanding of the disease and poor evidence behind each therapy. He identifies the clear need for greater scientific attention and research to improve outcomes for the suffering patients [1]

Non steroidal anti-inflammatory drugs

Marked symptomatic relief was seen with the introduction of NSAIDs. Though not a DMARD, its beneficial effects have been long documented with Willow and poplar bark, the substrates for salicylic acid, commonly used in the treatment of inflammatory arthopathies [10]. Aspirin was in use by the early twentieth century in the treatment of RA, making it the oldest of the medications currently in use [11]. We now have a vast selection of NSAIDs available, all working to inhibit the cyclo-oxygenase pathway.

Despite being effective analgesics and improving physical function, once thought to be serious challengers to the use of steroids in treating inflammatory arthropathies, NSAIDs have not had any demonstrable effect on disease course. Not without harm, the most predictable side-effects are of gastric irritation and nephrotoxicity [12].

Disease modifying anti-rheumatic drugs (DMARDs)

The term 'DMARD' appears to have been coined in the early 1980s; however the medications under this umbrella had been used well before. The term DMARD is applied to medications which can alter the course of disease and thus prevent joint erosion [13]. The mechanisms through which DMARDs act are varied but a collective outcome is to help stem the destructive process of intertwined inflammatory cascades resulting in the degradation of soft tissue, cartilage and bone.

DMARDs are broadly classified into two major classes,

Acupuncture; apple diet; auto-haemotherapy; angora wool
Bee venom; bangles, copper; Baths, various
Chemotherapy; copper salts; crows' meat; cobalt
Doca and ascorbic acid; diet
Extractions of teeth and other septic foci; ECT
Fasting; fever; faith; fango
Gin; guaiacum; gelatine; green-lipped mussel
Heat; honey; hope; hypnotism; hayseed
Insulin injections; iodine; inner cleanliness
Jaundice, induction of
K vitamin; kaolin compresses
Lourdes; love
Mud; magnetism; moxibustion; mistletoe
Nutmeg; nettles
Olive and other oils, oral and intra-articular
Placenta extracts; prayer; procaine; polyvinyl clothing
Quinine substitutes
Rhubarb; rest
Speransky's pump; sulphur; spa therapy; seaweed
Transfusions of blood, fresh or pregnant; tiger balm
Ultrasonics; underwear, anti-rheumatic; urea
Vitamins; vertebral manipulations; vaccines
Whale, standing inside; worms, earth-; water
Xmas snow
Yoghurt; yoga
Zam-Buk; Zyloric (allopurinol)

Figure 1 Historical treatments employed in RA [1].

synthetic and biological. Synthetic DMARDs can be further sub-classified into conventional synthetic or targeted synthetic. Conventional synthetic DMARDs are still the most commonly used agents for the treatment of RA, and include a wide array of drug classes, though the underlying mechanism of disease modification is not well understood. Targeted synthetic DMARDs, yet to be licensed in the European Union, contrast by antagonising specific markers implicated in the pathogenesis of RA. This newer class of drugs include the janus kinase (JAK) inhibitors (Jakinibs) (Figure 2) [4,14].

Prior to Glucocorticoids being acknowledged as a 'miracle drug' for RA, Gold and Sulpha containing drugs were recognised treatments for RA [12]. The 'infectious' reasoning (most arthropathies at the time being attributed to tuberculous infection) behind their use was largely due to the observed benefit in the reactive Poncets arthritis that can occur post-tuberculous infection. Though Gold therapy has been shown to be efficacious, its use has been largely limited by side-effects [4,15]. Glucocorticoids, though notorious for their extensive side effect profile, were for some time thought of as a cure for RA. As the evidence of multisystem effects from glucocorticoid use emerged, steroids came out of favour [6]; the emphasis was placed on treatment with medications to 'spare' the use of steroids. This drive, along with the understanding of RA and other autoimmune conditions, saw the emergence of a large range of disease-modifying medications. To date, they still represent the highest proportion of medications in use for RA patients and Methotrexate, the most common synthetic DMARD in use, remains the standard by which we measure effect of emerging drug therapies [16].

Early DMARDs

Glucocorticoids: The use of steroids as a treatment in inflammatory arthritis follows an intriguing course of events. In 1929, Hench et al from the Mayo Clinic made the observation of a 65 year old patient going into remission from his particularly stubborn RA after developing jaundice. Simultaneously Kendall, at the Mayo clinic, transferred his research interests from the thyroid to the largely unknown adrenal gland, whilst in Zurich Reichstein also began examining the organ. By 1935 the pair had extracted cortisone from the gland. In a reflection of the ever prevalent financial implications of medical discovery, the pharmaceutical firm of Merck Sharp and Dohme attempted to produce the substance in greater quantities for laboratory purposes and initially marketed the product at $1000/g [6]. By 1944, Dr Hench had documented similar remissions of RA to his original jaundiced patient in sixteen further patients. Having observed this in conditions extending beyond RA, including psoriatic arthritis and Myasthenia Gravis, the group concluded a substance X, possibly from the adrenal cortex, provided a group-specific benefit. The discovery of steroids, led to Hench, Kendall and Reichstein sharing the Nobel Prize in 1950. However, the well-documented side effect profile that soon became apparent from the use of steroids limited their popularity [6,17].

It was not until the 1980s that the beneficial effects of steroids were harnessed with lower dose preparations, resulting in an increase in prescriptions. Even now, steroids provide a highly effective form of treatment to induce rapid remission. Given the serious systemic side effects that patients have to endure with steroid use, the aim is to provide a bridging therapy to allow steroid sparing DMARDs to achieve maximal doses and efficacy without relapses [18].

Gold: Gold therapy was originally employed to successfully treat the Poncets arthritis that can occur with tuberculous disease. Employed in other arthritides as a result, the consensus being all arthritis had an infectious underlying cause, it became the first DMARD vindicated in the treatment of RA; the first favorable clinical study of 48 patients being published in 1932 [19]. This form of treatment was widely used for the coming decades. A slow acting agent, taking up to months to take effect, Gold has been shown to attenuate the destructive process in RA.

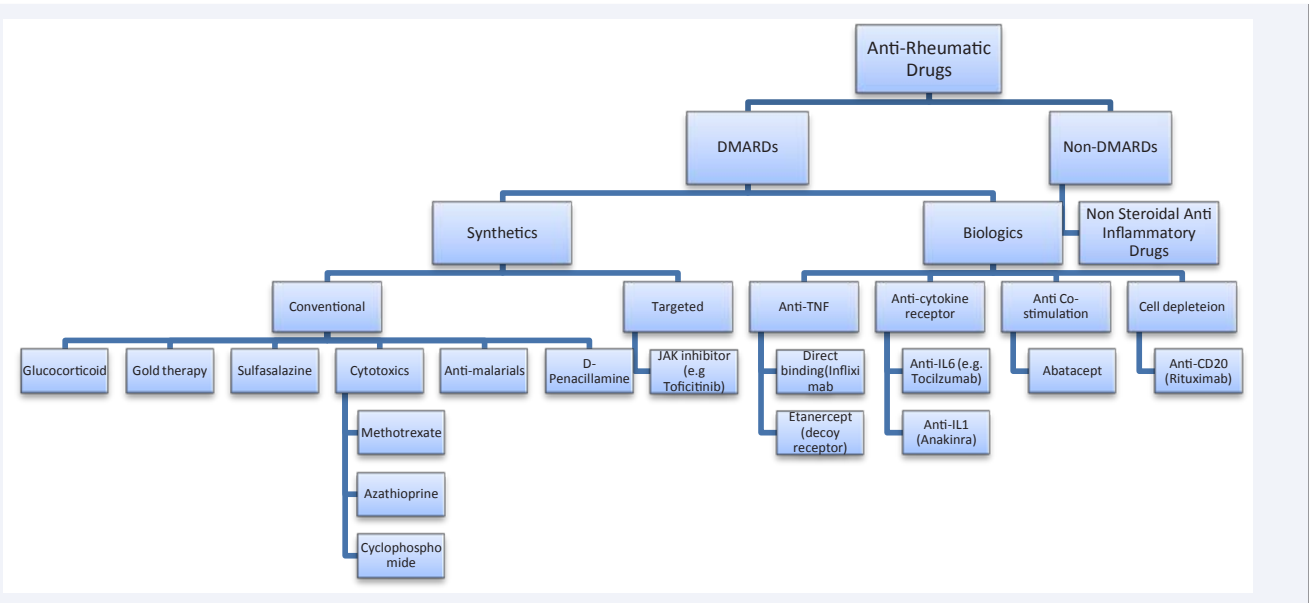

Figure 2 Classification of treatments for Rheumatoid Arthritis.

Its mechanism of action is not clear but it has been shown to decrease levels of COX-2, IL-6 and MMP-3 thought to be as a result of inhibition of MAP phosphatase-1 [20]. Though not commonly in use, Gold therapy is still for some patients the most effective mode of treatment. The intramuscular form of gold therapy has been shown to have comparable efficacy to Methotrexate, though its use is limited by side-effects, most commonly seen as a skin or mucocutaneous reaction, and more rarely a membranous glomerulonephritis or blood dyscrasia [13,15]. There are currently two intramuscular preparations of gold salts available (gold sodium thiomalate and gold sodium thioglucose) and one oral preparation (auranofin). The oral form is less effective and thus has been withdrawn from guidelines [15].

Sulfasalazine: After NSAIDs and Gold, Sulfasalazine (SSZ) is the third oldest drug class that is still available to use as a treatment of RA. In 1938, SSZ was the first drug to be synthesized specifically for RA. The consensus at the time was that RA was the result of infection and accordingly Svartz et al developed the DMARD, SSZ (originally known as salicylazosulfapyridin) by combining the anti-inflammatory, salicylic acid, with the antibacterial sulfapyridine by an azo bond [12].

It was initially shown to be effective in the treatment of RA, however Sinclair et al led a study discrediting its use in 1948. Subsequent analysis suggested the Sinclair study design was flawed but with the emergence of glucocorticoids, it was not until much later that enthusiasm for its use returned [12]. McConkey et al., demonstrated benefit in its use for RA in 1980, further studies confirming this to date [21]. With its prominent use for inflammatory bowel disease it is in the WHO list of Essential Medications [22].

Cytotoxic agents

Methotrexate: Methotrexate is a dihydrofolate reductase inhibitor, the mechanism through which it is thought to act as a chemotherapy agent. Its effect in RA however is thought to be multifactorial, with inhibition of cell maturation and more recently it has been demonstrated to show reduce TNF levels in synovial tissue of patients. Bronstein and colleagues propose this is in part due to augmentation of adenosine release through the inhibition of polyamines [23].

Until the introduction of Methotrexates precursor, aminopterin, Gold compounds were the standard for RA treatment. Developed initially as a chemotherapy agent by Farber et al, it was in fact a cardiologist in 1952, Dr Richard Gubner, who reported the beneficial effects of aminopterin in both RA and psoriatic arthritis patients [12,24]. The modified compound, Methotrexate, did not realise its potential in the treatment of RA till the early 1980s when a series of randomized controlled trials demonstrated benefit in refractory RA [12].

Methotrexate is now the drug of choice to maintain remission. Current European League against Rheumatism (EULAR) recommendations suggest therapy with a DMARD should be commenced on diagnosis of RA, with Methotrexate the preferred initial therapy unless contraindicated. Perseverance with the drug and escalation of dose is recommended to achieve maximal effect [25,26]. Further, escalation to maximal treatment doses is often not seen. Oral Methotrexate confers an estimated probability of 40.5% to result in adequate response and thus further therapeutic options have to be considered [27]. Despite non-response to Methotrexate, any escalation to a biologic is still recommended in combination with Methotrexate; studies have demonstrated combination therapy conferring greater efficacy than a biologic alone [28].

Azathioprine: Azathioprine is another cytotoxic agent in use in the treatment of RA. Originating from nitrogen mustard, an alkylating agent, this precursor had been employed in treatment of RA in 1951 [29]. Constructed as a pro-drug of the active metabolite 6-mercaptopurine, it acts to inhibit purine synthesis, resulting in the inhibition of lymphocyte proliferation and activity, thus having downstream effects of reduced immunoglobulin production and IL-2 secretion. First used in the early 1960s, efficacy has been demonstrated clinically in various studies but reduction in joint erosion has not always been consistent [30]. When compared to Methotrexate and Gold, it has been shown to be inferior and this has limited its use somewhat, most recently being removed from the EULAR recommendations for treatment of RA [15,16].

Cyclophosphamide: Cyclophosphamide, a further alkylating agent, was discovered by Brock in the 1950s [31]. Intended as an anti-cancer agent, it was originally shown to be effective in the treatment of RA in 1968 by Fosdick et al [32]. Efficacy has been shown in the use of cyclophosphamide in the treatment of RA but its use is currently limited to severe extra-articular manifestations. Of the conventional synthetic DMARDs, it was associated with greatest risk of infection related hospitalisation and is historically associated with bladder cancers [15].

Antimalarials

Quinine had been isolated in the 1920s by French pharmacists Caventou and Pelletier but the use of Peruvian bark, from which it is derived, had documented use in the treatment of fevers in the early 17th century [33]. Its use in the treatment of RA had been well documented by the early 1950s but its use became limited as a result of the supposed side effect of retinopathy [12].

Quinine derivatives such as chloroquine and hydroxychloroquinine are in fact very safe to use and further research demonstrated retinopathy as a rare side effect [34]. They are used commonly in the treatment of RA, but efficacy has not been demonstrated to be comparable to Methotrexate [15].

D-Penicillamine: D-Penicillamine was one of the earlier drugs to be trialled in RA as a result of advancements in understanding of the pathogenic mechanisms of the disease. In use as a copper chelator in the treatment of Wilson's disease since 1956, it was noted to result in immune complex dissociation and thus conferring application to RA, postulating a reduction in RF levels [35-36]. Though the first case to be treated with RA was demonstrated in 1963, more recently, no significant advantage was seen in the use of D-Penicillamine relative to placebo; this, in combination with its side-effects including bone marrow suppression, dysgeusia and gastrointestinal disturbance has limited its use [12,15,37-38]. Interestingly, one side effect of skin laxity has led to its use in the treatment of scleroderma [39].

Biologic agents

The renewed use of steroids and various synthetic DMARDs did not spell a period of inertia for the search for RA treatments. The history of monoclonal antibodies (mAb) provides an interesting story, and in some respects reflects the woes and joys of increasing commercialisation of therapeutic agents. The chimeric antibodies have murine and human portions reducing their immunogenicity. They differ from conventional synthetic DMARDs by providing an antigen binding site that directly targets a substrate thought to be involved in the pathogenesis of disease, allowing immune mediated depletion of the targeted substrate.

The drive in research into the immune system throughout the early 20th century led to the identification of a protective substance in serum against infections, more commonly known as antibodies. Behring and Ehrlich had, by 1939, popularised therapy with 'anti-sera' against infections such as diphtheria and pneumonia. Kohler and Milstein, Nobel Prize winners for their contribution to Medicine, went on to develop a process to produce large quantities of highly specific, standardised antibodies [40].

The interest in the therapeutic possibilities of these antibodies was substantial and rival companies, Centocor and Xoma, were formed to address specifically this. Drawing parallels to the early DMARDs, once again therapies were being developed for treatment of infections, and in this case to protect against septic shock [40].

By 1984, scientists had developed more stable and viable chimeric mAbs which led to the production of Centoxin, one of the early mAb, directed against bacterial endotoxin, marketed for the treatment of septic shock. Not only was this a costly product but it was subsequently shown to have little effect and harmful side-effects. With financial pressures to perform Centocor is said to have rushed its development and dissemination, with the initial trial shown to have flaws in study design and results reporting. Though optimism in the field of monoclonal antibodies waned, financial support for Centocor led to the production of various biologic agents, including abciximab, returning the company to financial viability and resurrecting enthusiasm in this field [40].

In 1975, Lloyd Old had discovered the cytokine, tumour necrosis factor (TNF) and Beutler et al went on to develop antibodies against this endotoxin induced substance to demonstrate protection against sepsis-inducing bacterial lipopolysaccharide [40,41]. This particular substance went on to be refined and marketed as Etanercept by Immunex [40].

Drs. Marc Feldmann and Ravinder Maini, studying the role of cytokines in the pathogenesis of RA, went on to run the first trial with monoclonal antibodies to TNF, Infliximab, in 1992 at the Kennedy Institute of Rheumatology which was at the time based at Imperial College, London demonstrated both positive clinical outcomes and a reduction in circulating inflammatory markers. These results led to it gaining FDA approval in 1999. As of 2015, the various anti-TNF agents had amassed total global sales of 25 billion dollars, making them the most profitable drug class [40,42].

We now have an array of biologic agents licensed for use against RA. They can target the cytokines by directly binding (Infliximab against TNF), work as decoy receptors (Etanercept against TNF) or target cytokine receptors (Anakinra against IL-1R and Tocilizumab against IL-6R). Biologics used in RA have been developed to target the CD20 molecule on B-cells leading to depletion (Rituximab) or against co-stimulatory molecules, such as CTLA4 (abatacept) [4,30].

Treatment guidelines suggest biologics should be used once response to DMARDs, one of which is usually Methotrexate, has been insufficient. TNF inhibitors are usually the first to be trialled but in some instances abatacept, tocilizumab or rituximab may be used, with similar efficacy shown in all these groups. The current recommendations suggest the use of a biologic should be in combination with Methotrexate; this is as a result of studies demonstrating benefit conferred to combination therapy when compared to mono-therapy, even in patients unresponsive to Methotrexate alone. Patients who have failed initial biologic therapy can be switched to an alternative one [4,16,28].

New non-biologic synthetics: the jakinibs

In 1995, Russell et al had predicted the possible future immunomodulatory role of JAK antagonism when reporting the mutation of JAK-3 in a patient with Severe combined Immunodeficiency [43]. JAK kinases, of which four types have been identified, phosphorylate cytokine receptors 1 and 2 on ligand binding, triggering downstream transcription factors [44]. This led to the development of drugs to specifically target this intracellular pathway, thus differing from the conventional synthetic DMARDs, mostly found to be effective in RA as a result of observational studies.

In 1998 Tofacitinib, the first of the JAK-inhibitors to be developed showed efficacy in mice models [45]. More recently in phase 3 trials, Tofacitinib has been shown to be effective in the treatment of RA and was approved by the FDA into 2012 [46]. JAK inhibitors have been shown to have efficacy in patients previously failing treatment on biologics and superior to Methotrexate in reducing signs and symptoms of RA, along with stemming the structural joint damage [46,47]. Safety profiles have demonstrated to show no increase in serious adverse events, and rate of other adverse events comparable to other DMARDs [48]. Of note however, the European Medical Agency did not approve its use, with a view that the potential risk of infections, cancers, gastrointestinal perforation and increase in cardiovascular risk, did not outweigh the clinical benefits [14].

DISCUSSION AND CONCLUSION

Rheumatoid arthritis is a destructive arthropathy that inflicts disabling and devastating effects on patients when kept unchecked. We have addressed the remarkable progression in treatments for RA over the last century and mostly in the last 30 years. Led initially by a theory of infectious aetiology, the successful therapies of Gold and Sulfasalazine were employed [12]. Glucocorticoids failed to provide the 'miracle cure' they promised, but are still essential to inducing rapid remission. They are commonly used and the rapid action provides the bridge for other DMARDs to reach efficacy recommended by EULAR guidelines in initial treatment [6,16,18]. The last 30 years have provided a rapid incline in the use and development of DMARDs.

Cytotoxics, namely Methotrexate, remain the cornerstone and a majority of patients have symptoms controlled with this group of medications, recommended in combination therapy even when monotherapy has failed [16].

As our understanding of the heterogenic pathogenic mechanisms underlying RA have developed, with a complex interplay of cytokines and cell mediated autoimmunity, we have seen the emergence of biologics and small-molecule non-biologics which have transformed the disease process for a large selection of patients providing a selection of 'step up' therapies [4].

There are, however, still unmet needs. It is estimated between 41-58% of patients do not achieve an American College of Rheumatology-20 response despite the use of biologics. A further group of patients, for reasons not known, lose responsiveness to therapies over time [49]. The Jakinibs have provided another treatment option and are likely to benefit a cohort of patients but are not without harm [14,44-48].

Trials are being run to assess the efficacy of drugs targeted to other implicated cytokines and immune pathways, namely granulocyte colony stimulating factor and IL-21 [4]. The heterogeneity of the disease amongst patient populations and differing response of individual patients to the various therapies suggests there is unlikely to be a 'one drug fits all' solution. It provides the opportunity for more tailored therapy for patients. As we understand the cytokine profiles and disease responsiveness of patient groups, drug selection could be customized to match patients earlier on in the disease [30].

We have now identified over 100 genetic loci conferring risk of RA. Okada et al identified numerous loci which code proteins already targeted by current therapeutic approaches. Characterising the remaining implicated risk loci will provide further insight into the pathogenesis of the disease and provide further targets for drug development, potentially tailored to an individual's genome [50]. Yarwood et al., go on to suggest as our understanding of the genetic basis for RA improves at an individual level, genome editing may provide a realistic option in the future [51].

Further, the pathogenic process appears to be in motion well before the disease appears to be clinically apparent. The current protocols suggest early treatment is ideal, and no doubt important, however tissue destruction is already apparent at this stage. Mechanisms to identify the patients in the period before the clinically apparent stage would provide a golden opportunity to stem the morbidity that ensues [4,52].

There has been a drive to minimise the systemic side effects seen with the immunosuppressive agents deployed. Treatment holidays can help give patients a relief and inducing drug free remission is always a target for patients [53]. As we understand why certain patients fail on particular therapies, tailoring drug regimens to particular patients may reduce the likelihood of receiving unnecessary medications and thus the side effects that accompany. Advances in drug delivery, such as the use of nanoparticles, targeting joint tissue to increase efficacy may also help to reduce systemic side effects [30].

The cost of biologic agents as of 2015 was reported between £9064 and £15,724.80 per year, depending on the biologic chosen [54]. With biosimilar agents to anti-TNF agents approved by the FDA and EMA, these costs are expected to decrease. No doubt this does however indicate the clear economic burden Rheumatoid Arthritis presents to Healthcare Systems and patients. This has to be evaluated in conjunction with the economic and social costs as a result of the underlying disease process, with 36-84% estimated to suffering work loss, underlining the need for effective early medical management [55].

As we discuss the drug treatment advances in RA, we cannot forget the advances in the patient-centred approach Dudley speaks of in 1974 [1]. The medical community strives to not only stem the disease process but manage the functional and psychological effects of having such a debilitating disease. Depression and anxiety have been associated with worse clinical outcomes in patients suffering with RA, underlining the need to effectively address mental health issues [56]. Further, the side effects seen from medications now available are not insignificant and thus require clinicians to remain vigilant and safe in the use of treatments. The astonishing advance in therapies introduced for RA in the last 30 years provides optimism but the need for more targeted and less toxic therapies is clear. This need will be best satisfied by combining current research into the aetiology of rheumatoid arthritis and evolving therapeutic techniques with reflection on past successes and failures in drug development, the aim to realistically strive for a cure.

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Cite this article

Aggarwal D, Abraham S (2016) Rheumatoid Arthritis Treatments: A Historical Perspective. JSM Arthritis 1(2): 1011.