WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Review of Disease-modifying Anti-Rheumatic drugs (DMARD) versus Conventional Synthetic DMARDs in Patients with Rheumatoid Arthritis

Manahil Zaman , Dr Sakib Khan , Muhammad Shahaan Shahid , Safia jan Aftab Qazi , Sara Iqram

Researchers Group NW institute Private Limited

Abstract

Rheumatoid arthritis is a chronic inflammatory condition affecting the joints of the body, thereby leading to reduced mobility and reduced life expectancy. Rheumatoid arthritis is commonly treated with disease-modifying anti-rheumatic drugs (DMARDs) among others. Other therapeutic alternatives include usage of conventional synthetic DMARDs and various other newer subclasses of DMARD-like drugs. The causative agent of rheumatoid arthritis remain unknown, though a strong link has been made to certain genetic factors and an environmental influence. Efficacy of treatment for rheumatoid arthritis is made by a combination of subjective and objective clinical examinations and imaging techniques.

Keywords: DMARDs, rheumatoid arthritis.

Introduction

This paper will review the usage and applicationof disease-modifying anti-rheumatic drugs (DMARDs) versus conventional synthetic DMARDs in the treatment of patients with rheumatoid arthritis. Rheumatoid arthritis (RA) is a systemic autoimmune condition, in which there is inflammatory processes both extra-articular and articular in origin. The disease follows a chronic course and primarily involves synovial joints in the body, e.g. elbow joint, hip joint etc. Articular involvement is often symmetric and can progress to several joints at once or separately, e.g. from elbow joint to radiocarpal (wrist) joint or to metacarpophalangeal (finger) joints. Chronic articular inflammation eventually leads to destruction and loss of bony cartilage and erosion of underlying bone, thus ultimately impacting mobility and life expectancy as a result[1].

Genetic Background

There is no known conclusive underlying factor for development of rheumatoid arthritis. In one study, an epigenetic link was made between genetics and rheumatoid arthritis through the influence of class II major histocompatibility complex (MHC) genes, specifically that of HLA-DR. HLA-DR is not always present in patients suffering from rheumatoid arthritis, but its presence signals an increased risk of severity and risk of mortality. However, this genetic link has been called into question as it has been noted that in case of identical twins, if one twin develops rheumatoid arthritis, there is an up to 15% less chance that their other twin will develop the disease as well. Therefore, the development of the disease is linkable not only to genetic basis, but also to environmental ones, e.g. smoking[2].

Pathogenesis

The pathogenesis of rheumatoid arthritis is a blend of complex environmental and genetic factors and their interactions with cytokines, predominantly CD4+ T cells (also known as T helper cells). CD4+ cells interact the autoimmune response with an arthritogen (i.e. an agent), postulated to be a chemically modified self-antigen or perhaps a microbial self-antigen. T cells then produce cytokines that stimulate other inflammatory processes. One is IFN-gamma produced by T helper cells that activates macrophages and synovial cells. Another is IL-17 from T_H17 which recruits new neutrophils and monocytes. Another is RANKL expressed on activated T cells that stimulates osteoclastic activity (thus leading to bone erosion), while another is TNF and IL-1, both of which stimulate macrophages in resident synovial cells to secrete proteases, ultimately leading to destruction of hyaline and articular cartilage in joints[3].

Treatment

The treatment of rheumatoid arthritis depends on a variety of factors, e.g. patient's accessibility and affordability of treatment options, severity of disease course and suitability of drug interaction with prevailing disease. Today, a common class of drugs used in treatment of rheumatoid arthritis are disease modifying anti-rheumatic drugs (DMARDs).

There are two main subtypes within this class. The first subclassis of conventional synthetic DMARDs:

- Apremilast: PDE4 inhibitor.
- Azathioprine: purine synthesis inhibitor.
- Ciclosporin: inhibits T cell activation.
- Cyclophosphamide: alkylates metabolites.
- Hydroxychloroquine: inhibits antigen and cytokine production.
- Leflunomid: inhibits pyrimidine synthesis.
- Methotrexate: inhibits dihydrofolate reductase used in DNA/RNA synthesis.
- Mycophenolate: inhabits inosine monophosphate dehydrogenase used in purine synthesis.
- Sulfasalazine: unknown; broken down into metabolites and act as anti-inflammatory agent.

The other subclass are of biologic DMARDs:

- Abatacept: binds to CD80, 86, to block T cell activation.
- Belimumab: inhibits B-cell activating factor.
- Ixekizumab: inhibits IL-17A.
- Rituximab: targets CD20.
- Sarilumab: IgG1 inhibitor.
- Secukinumab: IL-17A inhibitor.
- Tocilizumab: IL-6 inhibitor.
- Ustekinumab: IL-12 and Il-23 inhibitor.

There also exists another two newer classes of drugs, viz. TNF inhibitors (e.g. Adalimumab, Etanercept, Golimumab, Infliximab etc) and JAK inhibitors (e.g. Baricitinib, Tofacitinib etc)[4].

Efficacy of Treatment

Efficacy of treatment in rheumatoid arthritis is measured by a combination of subjective and clinical assessments, e.g. ACR (American College of Rheumatology) guidelines, DAS28 (disease activity score 28), CDAI (Clinical disease activity index) and imaging (MRI, CT etc). Patient report outcomes include HAQ (health assessment questionnaire) and ASES (arthritis self-efficacy scale). Physician and patient global measures are considered more sensitive, although none are numerically dominant as the following, viz. tender joint count, swollen joint count, grip strength, pain measures on a 10cm VAS (visual analogue scale) and functional status measure by PET (problem elicitation technique). HAQ is of moderate value in treatment. The least sensitive tools are morning stiffness, 5 point pain scale and ESR level[5]. ASES is closely linked to physical disability, pain, fatigue and disease duration and thus can be used to generally assess disease treatment plans[6].

In one network meta-analysis involving over 3,400 studies, early treatment of rheumatoid arthritis symptoms led to a higher rate of adverse side effects when using DMARD. Furthermore, use of traditional steroids concurrently did not paint a more negative therapeutic outlook for a patient[7]. In another network meta-analysis comparing biologics, DMARD monotherapy presented greater disease remission versus those using methotrexate[8].

For clinical interaction with patients, significant improvement was shown when disease management focused on decreasing pain, better life coping mechanisms (e.g. therapy, occupational therapy etc) and positive outlook on diagnosis. However, none of these factors have been lately measured in clinical trials, which instead focus on pharmacotherapy. Patients who participated in one study preferred health outcomes after treatment. However, treatment also depends on the patients' age, sex, time and magnitude of disease and insight among others[9]. In another systematic review and network meta-analysis, promising improvement were observed n DAS28 scores by utilizing tocilizumab, baricitinib and opinercept. In addition, usage of an 8mg/4w dose of tocilizumab was sighted as first choice drug in achieving disease remission[10].

As a whole, it remains hard to pin point desirable outcomes that most physicians would agree on in treatment of rheumatoid arthritis. Some regard decreasing joint damage, disability and improving mortality, while others utilize swollen joint count, tender joint count, acute-phase reactants. Some still prefer antibody titers and medical imaging techniques. For example, in the United States of America, MRIs are considered adequate evaluators of the disease. ACR20/50/70 scores are also used to evaluate changes during each clinical visit, while DAS28, HAQ, SDA and CDAI are used to measure disease activity in a particular moment in time[11]. According to one study in the case of pregnant females, DAS28 and CRP is a trust worthy metric[12].

Discussion

There is a great deal of radicalization in organization and treatment of rheumatoid arthritis after the first series of DMARDS, e.g. anti TNF-alpha drugs, came to the general market. Anti TNF-alpha inhibitors target TNF-alpha in general if conventional synthetic DMARDs are of little to no effect[13]. Furthermore in recent studies, it has been demonstrated that anti TNF-alpha drugs have little to no effect on heart condition, an underlying feature observed in elderly patients suffering from rheumatoid arthritis. In fact, anti TNF drugs given to high risk heart failure patients showed no increased symptoms while on such therapies[14].

Etanercept, another anti TNF drug, shows a higher margin of safety in patients with underlying heart conditions. In fact, in a double-blind RCT study on tocilizumab in European patients, there was a higher perceived tolerance and greater safety profile similar to other anti TNF drugs[15]. Furthermore, another study shows that blockage of IL-6 signaling is advantageous, as it predicts a reduced activity of the disease process in rheumatoid arthritis[16]. In a similar vein to IL-7 inhibitors, trials on olokizumab and levilimab (both IL-6 inhibitors), showed greater efficacy than the preceding IL-7 class targeter[17].

In a cohort study, efficacy of abatacept and adalimumab were compared and shows clinical efficacy of 64.8% in abatacept and 63.4% in adalimumab group, in comparison to methotrexate alone[18]. Similarly, in a randomized study comparing tafacitinib and adalimumab, it was observed that tafacitinib is as effective as adalimumab among patients who were given 5 to 10 mg of tafacitinib or Adalimumab per day. However, this also came with a higher risk of heart failure in patients[19].

Conventional synthetic DMARDs include cyclophosphamide, an anti-cancer drug similar to methotrexate, but which acts as an alkylator of cellular macromolecules thereby preventing cancer cell dissociation and spread as DNA is prevented from undergoing cell division in cancer cells. But cyclophosphamide carries extreme side effects, greater than that of methotrexate, thereby severely limiting its use[20].

Methotrexate, a drug commonly associated as an anti-cancer drug, is also widely used in treating rheumatoid arthritis. It is an anti-folate metabolite inhibitors, which blocks DNA synthesis, repair and cell replication. However, methotrexate is also associated with a much higher rate of adverse reactions in comparison to other DMARDs[21]. Leflunomide, a de novo pyrimidine synthesis inhibitor has a much impressive treatment course in comparison to both methotrexate and sulphasalazine[22].

A more tame drug in comparison would be sulfasalazine, which is commonly prescribed in individuals especially suffering from concurrent ailments, and whose safety profile is well-tested and tolerated. Unlike methotrexate and cyclophosphamide, the mechanism of action of sulfasalazine is unclear. Common adverse effects mainly concern the GIT, vomiting, diarrhea, dizziness, rashes etc. Moreover, sulfasalazine is associated with decreasing loss of bone and articular integrity. Similar drugs in this respect include minocycline, tacrolimus and hydroxychloroquine (which is in fact a malarial drug)[23].

Conflict of interest

The authors declare no conflict of interest.

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