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An Analytical Study Of Literature To Evaluate, "Does DMARDs Prevent Cartilage Degeneration In Rheumatoid Arthritis?"

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Abstract: *An analytical study was carried out to evaluate "Does DMARDs prevent cartilage degeneration in Rheumatoid Arthritis?". The study is a critical analysis of review of literature. The review was divided into three main parts viz. etio-pathogenesis of RA, drug profile of DMARDs, experimental and clinical studies which evaluate the effect of DMARDs on articular cartilage. It was found that exact etiology of the disease is not known and three probable causes are genetic, auto-immune disorders and infection. Synovial fibroblast is supposed to be a major target cell which by producing enzyme like MMPS, prostaglandin and nitric oxide accentuates the cartilage degeneration. Vascular Endothelial Growth Factor (VEGF) is also implicated as an important mediator for producing neo-vasculogenesis, pannus formation and thus cartilage degeneration. The role of COX-2, CXCR-4, IL-1RN, IL-6/8, MMP-10, MMP-12 and PLR-2 has already been established in RA. The two newer genes ADORA and BCL2A1 have been detected recently and are considered to be responsible for cartilage degeneration in RA. Experimentally and clinically all the DMARDs have shown to be effective in preventing and/or slowing the progression of cartilage degeneration. The remission brought with DMARDs in RA is consistent, reproducible and prolonged. Till date there is no evidence that DMARDs are able to regenerate the cartilage. DMARDs are effective in preventing cartilage degeneration when used early in the disease and when used as a combination therapy. So, to conclude the study it can be said that there are sufficient evidence clinically, radiologically and experimentally to that DMARDs prevent cartilage degeneration in Rheumatoid Arthritis.*

Key words: *DMARDS, Rheumatoid Arthritis, Cartilage degeneration.*

I. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease of adult which mainly affect the female sex. The disease damages various organs including the lungs, skin and heart but predominantly affect the synovial joint. Arthritis is the most common and dreaded manifestation of the disease and is responsible for maximum disability and morbidity. Most of the drugs in use are those which relieve the symptoms of the joint disease in RA.

Progressive destruction of articular cartilage and chronic inflammation of synovial joints are two main sequel of RA. As the disease progresses destruction of joint cartilage leads to loss of joint function and is responsible for the major disability in RA.

Two major groups of the drugs are used to relieve the symptom of disease viz. NSAID and DMARDs. DMARDs are further divided into conventional which include methotrexate etc. and biologics which include Tissue Necrotic Factor (TNF) inhibitor (etanarecept) and Inetrluekin(IL) inhibitor(anakinra).

With the advent of DMARDs and new biologics clinician today has much more flexibility for RA treatment. The mainstay of the research both clinically and experimentally is to evaluate the effect of drugs on cartilage degeneration. Although, DMARDs and Biologics have successfully achieved this aim nevertheless the affect is un-predictable and temporary at best. As RA is serious and disabling disease which primarily affects the joint cartilage and the synovial tissue and since there are many drugs regime available which claim to be affective on cartilage degeneration hence I undertook this review study to evaluate the literature to know the effect of DMARDs on cartilage degeneration. DMARDs have shown both clinically and experimentally the slowing of cartilage destruction but despite recent progress in controlling inflammation and cartilage degeneration little cartilage repair has yet to be observed.

The present study was thus undertaken to evaluate the literature of effect of DMARDs on cartilage degeneration and compare them with NSAIDs and SAIDs. The status of recent drugs like anti-TNF was also seen and there results were evaluated. The present status of research on RA was also reviewed. The study evaluated various clinical and experimental articles which highlighted the affect of DMARDs on articular cartilage. While going through the literature, one could learn that DMARD in various combinations improve the quality of life. However, clinically, radiologically and experimentally there is very little evidence of cartilage regeneration of DMARDs. Till date there is no pathological test available to forecast the severity of disease in

early stage. On top of it affect on cartilage is also short lived and fairly large number of patient ended up in total knee replacement. So this study was carried out to know the effectiveness of DMARDs in halting the progression of cartilage degeneration in RA.

II. Methods

The present review in study was to evalauate and critically analyse various article to know whether DMARD have any role in preventing degeneration of articular cartilage in RA. In the above context I reviewed and evaluated various articles which were clinical studies using EULAR or ACR parameter to assess the effectiveness of DMARDs and thus indirectly assess the effect on articular cartilage. I also evaluated the article which measured the radiological progression of joint space reducation as a parameter to evaluate the drug affect on articular cartilage. This evidence is supposed to be a direct evidence of drug affect on articular cartilage. In the present study I also reviewed many articles which experimentally determine the role of DMARD on chondrocytes, cytokines, chemokines and various RA genes which gave a insight on DMARD affectiveness on cartilage degeneration. The present study also evaluated various DMARDs, conventional and biologic and evaluated the result of various combination therapies used in RA. During the process of study a note was also made regarding the various theories of etiopathogenesis of RA and different biological markers used in experimental studies to evaluate the extent of cartilage degeneration.

A total of 13 studies which were primarily concerned with the study of effect of DMARDS on the disease progression of Rhematoid Arthritis were included. The observation cited were studied, their authenticity and drawbacks were evaluated and a final discussion was made based on information obtained from these articles. The study was concluded based on data and discussion carried out and was also based on author's own clinical experience.

III. Observation

The experimental study carried out by **Andreas**[(3)] observed that SAID is the most effective drugs which reverse the change to normal in human chondrocyte in RA. The study revealed that the DMARD have little role in the regeneration of the cartilage. The study observed the definite role of RASF and MMPS in cartilage degeneration. The study further observed that the best response was associated with marked suppression of IL-6, IL-23A, CCL-20, COX 2 enzymes in RA.

In vitro study by **Feihn et al**[(20)] observed the effect of MTX coupled with HSA (human soluble albumin) and observed that treatment with MTX or with MTX-HSA significantly prevent the cartilage destruction in the mouse model for RA.

In a study done by **Korpela et al**[(21)] to evaluate the long-term frequency of
disease remissions and the progression of joint damage in patients with early rheumatoid arthritis (RA) who were initially randomized to 2 years of treatment with either a combination of 3 disease-modifying antirheumatic drugs (DMARDs) or a single DMARD. In this multicenter prospective followup study, a cohort of 195 patients with early, clinically active RA was randomly assigned to treatment with a combination of methotrexate, sulfasalazine, hydroxychloroquine, and prednisolone or with a single DMARD (initially, sulfasalazine) with or without prednisolone. After 2 years, the DMARD and prednisolone treatments became unrestricted, but were still targeted toward remission. The long-term effectiveness was assessed by recording the frequency of remissions and the extent of joint damage seen on radiographs of the hands and feet obtained annually up to 5 years. Radiographs were assessed by the Larsen score.

A total of 160 patients (78 in the combination group and 82 in the single group) completed the 5-year extension study. At 2 years, 40% of the patients in the combination-DMARD group and 18% in the single-DMARD group had achieved remission ($P < 0.009$). At 5 years, the corresponding percentages were increased to 28% and 22% (P not significant). The median Larsen radiologic damage scores at baseline, 2 years, and 5 years in the combination-DMARD and single-DMARD groups were 0 and 2 (P _ 0.50), 4 and 12 (P _ 0.005), and 11 and 24 (P _ 0.001), respectively.

They concluded that aggressive initial treatment of early RA with the combination of 3 DMARDs for the first 2 years limits the peripheral joint damage for at least 5 years. The results confirmed the earlier concept that triple therapy with combinations of DMARDs contributes to an improved long-term radiologic outcome in patients with early and clinically active RA.

In a longitudinal study done by **Niki et al**[(4)]**,** analyzed levels of serum cartilage biomarkers during 54 weeks of infliximab therapy, to evaluate the feasibility of biomarkers for monitoring structural joint damage. Their study comprised 33 patients with early RA and 33 patients with established RA. All patients received 3 mg/kg of infliximab and methotrexate for 54 weeks. Levels of the following serum cartilage markers were measured at baseline and at weeks 14, 22, and 54: hyaluronan (HA); cartilage oligometric matrix protein (COMP); type II collagen (CII)-related neoepitope (C2C); type II procollagen carboxy-propeptide (CPII); and

keratin sulfate (KS). Time courses for each biomarker were assessed, and relationships between these biomarkers and clinical or radiographic parameters generally used for RA
were investigated. The final observation in this article revealed that biologic marker are more sensitive and accurate parameter in RA and it observed the reduction in level of biologic markers after use of DMARDs and further observed that this is associated with decrease in cartilage degeneration. The study also observed that new biological marker like HA, COMP, C2C, CP II, KSYRL40 are effective in measuring articular degeneration. During their study they observed that the higher course of C2C, CP II level during anti TNF therapy indicated a shift toward CII synthesis in early RA. This observation was not seen in established RA probably due to irreversible cartilage damage in late cases of RA. This observation is significant since it further confirms that DMARDs are useful when started early in the course of RA disease. The study observed that DC2C/CP II offer a useful marker while assessing the extent of joint damage and is independent of other indices like MMP-3.

In their experimental study **Kraan et al**[22] observed that activated T cells in RA are suppressed by Leflunomide. However, they find no change in IL-6 levels after the use of leflunomide. The study further showed that IL-6 and IFN levels were significantly reduced after the MTX treatment. These observations confirm the hypothesis that these cells are inhibited by Leflunomide and drug is highly selective on this action.

Neieminen et al[23] observed experimentally that gold compounds (auro thiomalate) act as anti-inflammatory agent by increasing the expression of MPK-1 and thus suppressing the COX-2, MMP3 and IL-6.

Nagashima et al[2] observed that BUC and GST(gold sodium thiomalate) inhibit the production of VEGF both when given alone and in combination. The study observed that MTX and DEX also inhibit the VEGF production. The study observed that none of the DMARDs or DEX inhibit bFGF(basic fibroblast growth factor) when given alone but a combination of SASP and GST inhibit the production of bFGF in their experimental study. The finding is significant as it further affirm that the combination of the drug is superior to single drug therapy.

Paula et al[1] in their article observed the effectiveness of biologics using ACR criteria. He observed that Abatacept and Tocilizumab has best ACR50 response while Anakinra has the worst response.

In his study **Andreas**[3] observed complete reversal of RA related gene with SAID. DMARD has a moderate affect and chloroquine has a minimal affect. The article observed that among the DMARDs, MTX has the best affect. The author observed that production of MMPS, prostaglandin and nitric oxide are three major pathways through which cartilage degeneration take place. The author observed that evidence of regeneration of cartilage till date is indirect and he observed that the GTCF and CYR-61 factors are associated with cartilage regeneration and needed further research and experimental and clinical trials on these two factors.

A very comprehensive clinical study[5] was carried out using clinical criteria for improvement based on ACR, radiologic progression of disease and comparison was made among various combination of DMARDs including biologic DMARDs and the results of this study are shown in. As observerd in table there is no significant difference between various combination but there is slight increase in complication rate with biologic DMARDs and Anakinra in particular. It also showed that the wound healing is delayed with steroidal drugs which by far is most effective in relieving the symptoms. The observation in the above table showed no difference in various drugs in each subgroups of DMARD.

IV. Discussion

RA is one of the most disabling systemic disorder affecting mainly the female sex in adult and middle age group. The disease primarily attacks the synovial joints which results into a prolonged and permanent disability in patient. The disease also affects other organs of the body including the cardiac, the renal and the hepatic functions of our body. The disease is a systemic disease but the cardinal and most pronounced symptom of the disease is cartilage degeneration affecting the major joints like the knee, the hip, the wrist and the elbow and the joints of the hand.

If one sees the natural history of the disease, the progression of the disease is variable and only one-thirds of the patients ended up in serious degenerative disorders leading to a compromised life style and the quality of life is also seriously affected in the patients of RA. In rest of the patients the affect of the disease is moderate which respond to drug therapy and alteration in the lifestyle including physiotherapy etc.

While reviewing the history of drug therapy the mainstay of the drug therapy in the earlier part of the century was confined to the non-steroidal anti inflammatory drugs which resulted into moderate affect and never ever halted the progression of the cartilage degeneration. The continuous and prolonged use of NSAIDs resulted into renal problems and serious GIT disorders. The drug discontinuation was a common occurrence. The earliest DMARDs mentioned in the literature is that of the gold therapy used as an injectable preparation which gave very variable results and the toxicity was more often and as the side effects were outweighing the benefits the drug never became popular. With the advent of steroid anti inflammatory drug the results showed remarkable improvement in the symptoms of disease and patient returned to a normal functional status in very short period.

However the complications associated with SAIDs were again serious, permanent and the drug needed continuous in its dosage schedule which cause further systemic complications.

MTX was the first effective and tolerable Disease modifying anti-rheumatic drug which gave prolonged, sustained and reproducible results in a dose which was least toxic to the patient. With the success of MTX many more drugs came into and the physician has now much more flexibility and his armamentarium is now full of many drugs which he can use alone or in combination with better results. The advent of anti-TNF or the Biologics has opened a new field in the treatment of RA, their results are promising but their major drawbacks are serious side effects and parenteral mode of administration.

As the drug therapy is improving so is the understanding of the etio-pathognesis of the RA is gaining momentum. Initially RA was considered as an inflammatory disorder but with the advancement of newer technology including that of the molecular science, the understanding of the disease has advanced. The disease is now considered to be caused by three major factors including that of genetics, infective and auto-immune disorders. The environmental effect including that of the smoking is considered to be important one. There are now more than 110 genes recognized as the RA causing genes which play important role in producing the disorders. The association of periodontitis caused by porphyromonas have also been linked with RA. The detection of auto-antibodies produced by the B-cells have almost established the etiology of the disease. Various studies have confirmed that activated B-cells in RA and their suppression by various drugs both experimentally and clinically results in reduction is disease activity. However, all these factors are presumptive and till date no direct evidence is available which pin-point the etiology of the disease. The role of B-cells as well as the T-cells is well established but what activates them is not yet known. Similarly the location of the hundreds of RA genes further confuses the already perplexed disease as far as the etiology is concerned. Smoking has been linked as an important environmental factor but the disease is more common in female but the incidence of smoking is less common in women more so in asian population. Recent cell technology and enzyme assays have revealed the major pathways for producing RA. These include the prostaglandins, MMPS and nitric oxide which form a major pathway in producing the cartilage degeneration and thus the disease symptomatolgy.

The detection of Tumor necrosis factors (TNF) and various Interleukin (IL) further enhance our knowledge as to the pathogenesis of the disorders in RA. Till very late, the only diagnostic tool available to diagnose the disease was to detect rheumatoid antibody factor popularly known as RA factor, raised erythrocyte sedimentation rate (ESR), and C-reactive proteins. With the advent of new biological markers the diagnosis has become more accurate and fast. The newer markers like anti- CCP has revolutionized the diagnosis of RA as this marker is detectable very early in the disease and established that in particular patient immunity factor or B-cell activation is more pronounced. The more recent biologic markers like HA, C2C, CPII etc are still in experimental stage but they in future will tell extent of cartilage degeneration and will help in evaluating the drug effectiveness in more objective way.

In RA since the major defect is the degeneration of the cartilage and the various drugs primarily affect the articular cartilage and since most of the studies also ascertain the effectiveness of particular drug by measuring the affect on articular cartilage I undertook the present study which is a review and analytical study to review and analyze the role of present DMARDs on articular cartilage and to see whether these drugs have any positive role in preventing cartilage degeneration and/or do these drugs have any role in regeneration of the cartilage.

The effectiveness of the DMRADs were evaluated using the clinical parameters like pain, swelling and restriction of the activity were the basis of the effectiveness of the drug. There were other studies mostly experimental which ascertain the affect of DMARDs on various cytokines and expression of gene and their affect on various cells of inflammation. Most of the in vitro studies concluded that DMARD suppresses the genes of the RA and also suppress the activity of various cytokines and chemokines. However, most of these experimental studies did not correlate with the clinical suppression of the disease and vice-versa too and hence the results were mostly presumptive at the best. Similarly in clinical trials the affect on the degeneration of cartilage is measured by measuring the pain, range of movement and in some studies by radiological evidence of degeneration of cartilage. These parameters are again subjective and they do not tell which patient has actually being benefitted by the use of DMARD since there is a reported spontaneous remission in 14 % of cases while by using the DMARDs the remission rate is 18%. The drugs trials are also not very cohesive and their meta-analysis raised more questions than solving the problem.

An in-vitro experimental study was being carried out by **Andreas**[(3)] et al in which human chondrocytes were cultured from the synovial fibroblast from healthy and RA individual. These were treated with DMARD, NSAID and SAID. In this study the chondrocyte gene profile was determined using micro-arrays real time RT-PCR and ELISA to validate the datas. The result showed that SAID was the most efficient to reverse the disease to healthy pattern. It was followed by DMARD and NSAID. The clinical forsight also correlate well with the experimental studies result as the quickest and most affective results are obtained by the use of dexamethasone which is followed by DMARDs. However the present study was mainly experimental, it did not reveal any

chondrocyte regeneration by the use of DMARD. In the present study the cytokines and various genes recognized during the process were also found to be associated with other inflammatory disorders and hence the study could not be considered to be very specific. The present study however affirmed the definite role of RASF and MMPS in cartilage degeneration. The present study is helpful in detecting the various target genes, cytokines and chemokines which are activated by activated in RA and will help in developing the future drugs in RA.

Development of biological markers are another important research tool which on one hand gave the extent of tissue damage and on the other hand helping in the diagnosis the disease and in a definitive way.

Niki[(4)] et al in their study analyzed the level of serum cartilage biomarkers. Their observation revealed that the biological markers are more sensitive and accurate parameter of joint damage in RA. The study developed new biologic markers like COMP, C2C, CPII, KSYRL 40. These markers are raised early in the disease and are almost specific to cartilage degeneration. The development of these newer biological markers are important in understanding the basic pathogenesis of cartilage degeneration and probably in newer future more accurate and sensitive markers will be developed which will help in forecasting the severity of the disease in early stage, diagnosing the disease at the beginning and evaluating the effect of various DMARDs in RA in relation to articular cartilage degeneration.

Andreas[(3)] has studied extensively the pathogenesis of the disease and through his experimental studies stressed and confirmed the role MMPS, prostaglandins and nitric oxide as the major pathways through which the cartilage degeneration take place. The importance of these factor are that in due course of time the drug could be developed which affect these three factors and probably will help in curing the RA. In contrast to these factors, two other factors were also detected namely GTCF and CYR61 which showed some correlation with cartilage regeneration. However so far these findings are at a very premature stage and no drug has yet been developed which enhance the activity of this factor.

Nagashima[(2)] demonstrated another important factor named VEGF as produced by the platelet endothelium. The activity of this factor is enhanced in RA. The importance of this factor is that this factor is suppressed by Bucillamine and GST but is not affected by MTX alone. The detection of this factor and selective inhibition of this factor by only few drugs shows why a single drug is not affective in RA and that's why combination of DMARD is more affective than single drug therapy.

Table 1 describes various available DMARDs and described their affect in a table form which showed that most of the DMARDs show their affect after two or three months of treatment. The table also showed the toxicity of each drug which should be kept in mind and monitored during the course of treatment with these drugs. They also showed through its table that only few of the anti- tumor necrotic factor drugs are approved by FDA. These drugs include infliximab, etaneracept, anakinra and adalimumab. It also showed the chemical properties of each anti- TNF drug and concluded that most of these drugs are affective in relieving the symptoms in RA either as single or in combination with DMARDs.

While evaluating the effect of drugs in RA two clinical criteria have been developed, one is ACR response criterion and another one is EULAR criteria. Both these criteria use clinical parameters mainly pertaining to the joint conditions, the affect on activity of daily living and also take into consideration the laboratory investigation including the CRP and anti-CCP. These two parameters help in assessing the drug affect objectively. In ACR, the response by the drug is divided into three categories, ACR20, 50 and 70.

While reviewing the effectiveness of various DMARDs on joint cartilage and thus relieving the symptom of the disease I found that the literature is abundant and most of the studies demonstrated that the role of DMARDs in halting the progression of cartilage degeneration is positive, prolonged and outweigh the side effects produced by these drugs.

Korpela[(21)] et al evaluated the long term frequency of the disease remission and concluded that when started early with two or three drugs of the DMARDs showed much better results than with those who started late and are confined to single drugs. This study use combination of MTX, SSZ and HCQ with or without prednisolone. The result showed that the drug limit the peripheral joint damage for atleast 5 years.

Kraan[(22)] et al studied the effect of leflunomide and MTX in RA in their experimental studies. This study shows that by using MTX and Leflunomide, the activated T cells remains suppressed for long period which is a source of inflammatory cells and cause of production of pannus in RA.

Neinemenen[(23)] et al observed in their experimental study that gold compound aurothiomalate is effective in reducing the inflammation by reducing the expression of MPK1 and their by suppressing the COX and IL-6. The result of this study goes well with our clinical hindsight as gold therapies is one of the oldest DMARD used in RA.

While reviewing the various studies as shown by **Schwarzer** et al, in a multicentre study **COBRA** trial and later by **Rau** et al that the combination therapy is superior to a single therapy in relieving the cartilage symptoms. These studies further revealed that MTX is the mainstay of the treatment in RA. The result of these studies further confirms that there are variable etiopathological factors working simultaneously in RA. By using

a combination therapy for eg. MTX and leflunomide the activity of bith b cells and T cells are suppressed i.e. to further elucidate the we can say the by using a combination of the drugs, the anti-inflammatory and immunity factors are simultaneously taken care of. The only drawback of using the combination therapy is that the body defence mechanism is markedly reduced and which invite serious secondary secondary infections. The drug monitoring is also difficult and at times costly. Each drug has its side effect and toxicity which has to be monitored clinically and by laboratory investigations. While reviewing the various DMARDs it was found that AZA has the maximum toxicity among the conventional DMARDs and as such is not a drug of choice and in any case should never be used in combination with MTX (**Wilkins 1992**).

The study also revealed that the antimalarial drugs is one of the least affective DMARD. This drug in addition has much more side effect including that of retinopathy which although is rare and develops after more than 5 years of use. Leflunomide is one of the most effective DMARDs and can be used in combination with other DMARDs without much side effect. This quality of this drug is probably due to least effect on bone marrow, skin and GIT. The role of anti TNF drugs has generated much of the excitement and is one of the most extensively researched drugs both experimentally and clinically. The drug has been studied by **Paula[(1)]** in his experimental study and they concluded that drug act both on T cells and B cells and thus these drugs are highly affective in relieving the symptoms in RA. It is because of these qualities that these are considered to be more superior as far as their inhibitory role on cartilage degeneration is concerned.

In a multicentre phase II trial, TNF antagonist have shown superior results where the MTX is ineffective. These biologics consist of two groups, anti TNF and more recent anti –IL drugs. Anti TNF are further sub grouped into etaneracept and infliximab. Although there chemical configuration is different but their side effects are common hence they are studied as common group. As shown in table no 5 the result showed that the various drugs in their subgroups have more or less common affect and there is very little to choose one from another. However, few other studies have shown the results which are contradictory to the above statement.

Paula[(1)] has shown that the role of rituximab is superior to other drugs in same subgroup but **Winblatt[(18)]** et al in their large clinical study has shown that the results of MTX with etaneracept and the result of MTX with infliximab are more or less same. He has further stated tthat till date there is no head to head comparison between infliximab and eteneracept. Although the WHO has in its guidelines **()** has advised to use these drugs in only those patients where MTX has failed where the disease is very severe which is in contrast to what US FDA has approved these drugs as first line of drugs. Again in contrats to the US FDA the European Medical Pharmacopeia approved this drug only when other DMARD has failed. All these studies have further confirmed that anti-TNF does have a very affective and lasting effect on halting the cartilage degeneration and thus relieving the symptom of the disease but at the same time these drugs are highly toxic with serious side effects including that of the bone marrow suppression, serious secondary infections, disabling infusion site discomfort and thus they should be used with caution and in selective patients. In spite of their effectiveness they still have a limited role in advanced RA and when used late in the disease. Thus, although they are a group apart and have shown promising results, but as the evidence shows they are not much superior to other DMARDs.

Another biologics are anti IL which is divided into two main groups viz. anti-IL1 i.e. Anakinra and anti- IL 6 i.e Tocilizumab. The study revealed that these two drugs are although affective but out of these two Anakinra have serious side effect when used alone or in combination with MTX and have thus gone out of the favor. The common side effects of these drugs are reactivation of tuberculosis and hepatitis B. Thus again these drugs should be used with caution and only in those cases where other DMARD have failed to give results.

Thus, the present clinical and experimental study review have shown that RA is a multi-organ multisystem disease caused by multiple etiological factors and developed in the body through multiple pathways mediated by T and B cells producing multiple enzymes like MMPS, prostaglandins and Nitric oxide. The disease is progressed and the disease activity is maintained through activation of multiple RA genes and cytokines like IL 1 and 6 which results into articular cartilage degeneration and a classic clinical disaease. The conventional and biologic DMARDs have a significant role in affecting the various etio-pathological factors and halting the degeneration of articular cartilage. The review of the study has shown that HCQ is least affective while MTX is the most affective DMARD till date. The combination is superior to monotherapy in DMARDs. Anti TNF drugs although are very affective on halting the degeneration of articular cartilage but are toxic and should be used in serious conditions only. This review study showed that the future research should target the factors like GTCF and CYR61 which have shown promise in regenerating the denuded articular cartilage. The study thus answer the question whether DMARD has a role in preventing degeneration of articular cartilage in RA in positive way i.e. the DMARD does prevent the degeneration of articular cartilage when used in RA at early stage.

V. Summary And Conclusions

- An analytical study was carried out to evaluate "Does DMARDs prevent cartilage degeneration in Rheumatoid Arthritis?"
- This study is presented for submission to University of Buckingham as a part of curriculum for MD in General Internal Medicine.
- The study is a critical analysis of review of literature.
- The review was divided into three main parts viz. etio-pathogenesis of RA, drug profile of DMARDs, experimental and clinical studies which evaluate the effect of DMARDs on articular cartilage.
- The present study was undertaken as RA is one of the most common serious ailments which have profound effect on socio-economic status of patient and his/her family.
- The disease is one of the major causes of the permanent disability of the limbs and in particular of major joints and results in significant disability and morbidity.
- During study it was found that exact etiology of the disease is not known and three probable causes are genetic, auto-immune disorders and infection.
- Environmental factor has also been described as causative agent.
- Each causative factor has both supporting and opposing evidences and hence the etiology of the disease has remained a dilemma till date.
- The pathogenesis of the disease has been extensively researched and this mystery has been unlocked due to some path breaking experimental studies.
- RA is considered as an auto-immune disorder with super-added element of inflammatory process.
- Synovial fibroblast is supposed to be a major target cell which by producing enzyme like MMPS, prostaglandin and nitric oxide accentuates the cartilage degeneration.
- Vascular Endothelial Growth Factor (VEGF) is also implicated as an important mediator for producing neo-vasculogenesis, pannus formation and thus cartilage degeneration.
- The molecular science has brought various new factors which include cytokines and chemokines and are responsible for persistence of disease in body.
- The study found that 110 RA genes being present in chondrocyte of the RA patient.
- The role of COX-2, CXCR-4, IL-1RN, IL-6/8, MMP-10, MMP-12 and PLR-2 has already been established in RA.
- The two newer genes ADORA and BCL2A1 have been detected recently and are considered to be responsible for cartilage degeneration in RA.
- The new biological markers have helped in identifying the disease earlier and are also suggestive of cartilage degeneration. These newer biological markers except anti-CCP are at present in experimental stage only.
- DMARDs divided into conventional and biologics.
- Out of conventional DMARDs, chloroquine is least effective and methotrexate is most effective.
- Combination treatment with DMARDs is most effective and mono therapy is less effective.
- Leflunomide is one of the safest DMARD and can be combined with most other drugs because of its least toxicity.
- Biologic drugs are also divided into; anti-TNF drugs which include Etaneracept and Infliximab and IL antagonist which include anti-IL1 Anakinra and anti-IL6 Tocilizumab.
- These biologic drugs are effective but their toxicity and safety standards are not yet well established.
- The biologic drugs are recommended to be used in serious RA disease and or whenever the methotrexate is ineffective.
- USA is the only country where these drugs are being used as first line drug.
- Experimentally and clinically all the DMARDs have shown to be effective in preventing and/or slowing the progression of cartilage degeneration.
- The remission brought with DMARDs in RA is consistent, reproducible and prolonged.
- Till date there is no evidence that DMARDs are able to regenerate the cartilage.
- DMARDs are effective in preventing cartilage degeneration when used early in the disease and when used as a combination therapy.
- So, to conclude the study it can be said that there are sufficient evidence clinically, radiologically and experimentally to that DMARDs prevent cartilage degeneration in Rheumatoid Arthritis.

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