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Expert's Approach of Neoplasms in the Most Ubiquitous Autoimmune Rheumatic Disease



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ABSTRACT

Rheumatoid Arthritis is a chronic & disabling polyarthritis disease which affects mainly women in middle & old age. Functional impairment & irreversible joint deformities is caused by the Rheumatoid Arthritis. Rheumatoid arthritis is linked with the autoimmune diseases such as multiple sclerosis, type -1 diabetes mellitus & asthma. Most likely as a response to unknown exogenous or endogenous antigens, the CD₄⁺ and T-cells are involved in the induction of rheumatoid arthritis. Other cells like as monocytes, macrophages & fibroblast produce cytokines such as tumor necrosis factor - α (TNF - α)& interleukin-1 without the synovial cavity. This cytokine is central to damaging cascades, ultimately triggering the production of matrix metalloproteinases & osteoclast which results in irreversible damage to soft tissue & bones which cause rheumatic arthritis. Further damage & complement fixation may cause by the improper regulation of the β -lymphocytes. Several new drugs have become available for the treatment of rheumatoid arthritis in this article.



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INTRODUCTION

Rheumatologist have developed & proved many essential changes in the treatment of RA for many years, targeted to improve outcomes & reduction in the risk of organ damage[1-7].

Since the sex hormone plays an important role in disease development & course, it is more prevalent in women. The increase of free steroid hormones like glucocorticoids, Progesterone & Oestrogen induces changes in functions of immune competent cell such as β cell, T cells & monocytes, which results in clinical symptoms of immune mediated Rheumatic Arthritis [8].

An interesting topic is to understand the role of vitamin D supplementation which prevents cancer & autoimmune disease that results in the reduction of total mortality rate [9].

Vessels & the vascular endothelium are involved in the pathogenesis of inflammatory rheumatic diseases. It serves as a prototype of this disease on which much more data are available regarding leukocyte recruitment into the synovium, angiogenesis& accelerated atherosclerosis [10, 11].

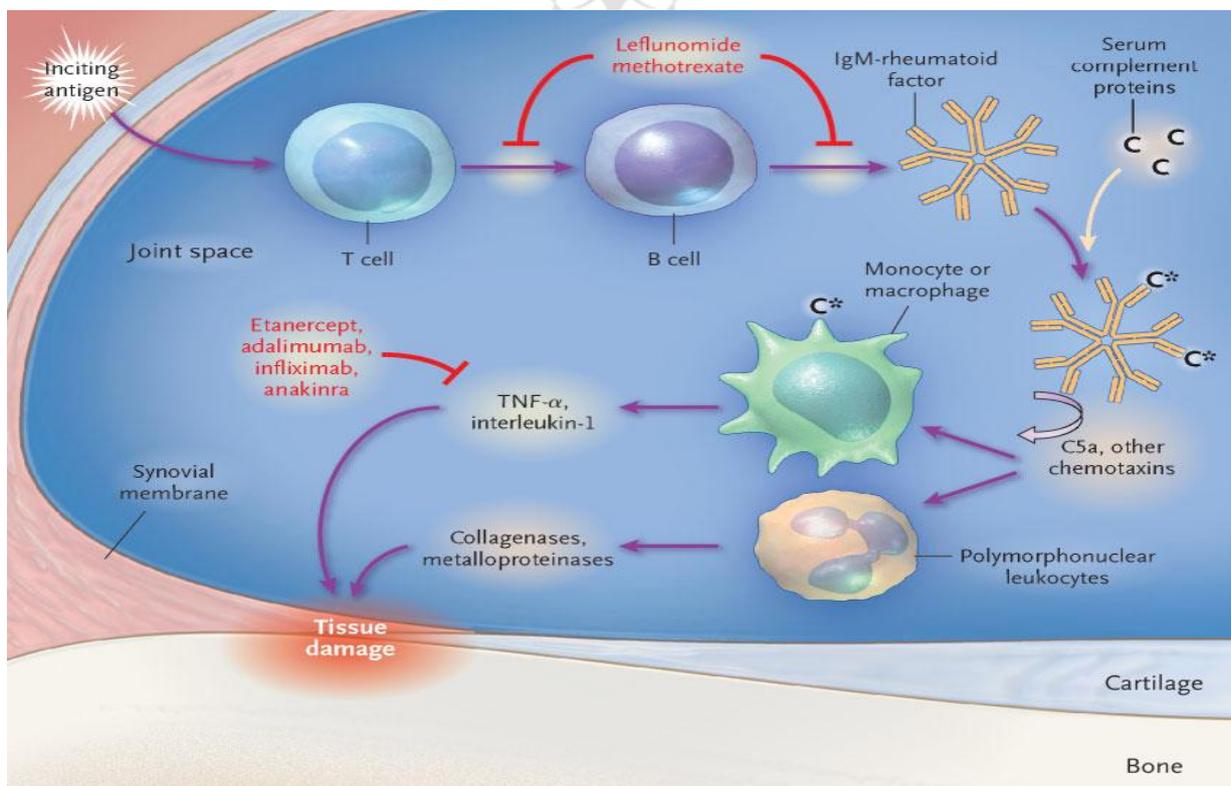


Figure 1. Inflammation in the Rheumatoid Joint.

Rheumatoid arthritis is a chronic inflammatory joint disease, which affects millions of people all around the world, with a prevalence rate ranging from 0.5 to 1% [12].

The identity of the inciting antigen is not known, but it most likely drives lymphocyte proliferation, which contributes to the production of the rheumatoid-factor autoantibody. The fixation of complement amplifies the destructive cascade, attracting additional inflammatory cells and resulting in the production of cytokines and enzymes. These, in turn, immediate tissue damage, including cartilage loss and bone erosion. Likely sites of action of the major drugs described in this article are shown. C denotes serum complement protein, and C* activated serum complement protein.

SELECTION OF STUDIES

The analysis of the titles & abstract according to eligibility criteria was perfect by two independent reviewers. In case of disagreement, that they were analyzed by a third reviewer.

3. Autoimmune Diseases:

Many autoimmune diseases develop because of an immune system response. Davidson & Diamond define such diseases as “a clinical syndrome caused by the activation of T cells & β cells, or both, in the absence of an ongoing infection or other distinct cause”. They may develop sometimes either after an infection or after vaccinations [13, 14].

Studies on Several Autoimmune diseases

I. Multiple Sclerosis (MS)

The increase in the widespread of Multiple Sclerosis is increasing with altitude, which has been confirmed in later War periods [15, 16]. Once Multiple sclerosis develops, short wave ultraviolet B(UVB) & vitamin D can reduce the severity of disease by inducing apoptosis of CD₄ T lymphocytes [17].

Seasonality risk data for Multiple Sclerosis has been established during the time of entry into the world War II & Korean conflict [16] that reveals the solar ultraviolet B levels in the US are asymmetrical [18] for two important reasons:

- The surface elevation is generally higher from the Rocky Mountains to the west.
- The ozone layer is thinner because of the prevailing westerly winds crossing the Rocky Mountains & pushing the tropopause.

II. Type 1 Diabetes mellitus

Type 1 diabetes is another autoimmune disease linked to viral infections [19, 20] & low vitamin D intake [21] & low serum calcidiol level [22]. A significantly increased risk was observed for illness in the neonatal period. The epidemiologic features of Type 1 Diabetes Mellitus are similar to Multiple Sclerosis since the prevalence is increased with the increasing latitude in Australia [23].

III. Asthma

Another highly risked autoimmune disease is prevalent during pregnancy so, vitamin D supplementation in infancy correlated with increased risk of asthma in adulthood, which shows protective effect in other but an adverse effect in infancy [24-29,30]. Vitamin D reduces the risk of asthma, which has the strongest evidence that vitamin D reduces the risk of viral infection since they are associated with about half of all the cases of adult asthma [26,29,31].

4. Pathogenesis

An agreement of general scientific exists, which consider Rheumatoid Arthritis as an immune mediated disease that could be possibly be triggered by an environment (microbial) factor in a genetically susceptible individual.

Some of these listed evidences supports the role of cellular humoral autoimmunity in the development of Rheumatoid Arthritis.

i) The Major role of β lymphocytes in the pathogenesis of Rheumatoid Arthritis [32] & signs of accumulation of immunoglobulin & other inflammatory products such as complements on the site of synovial pathological lesions in Rheumatoid Arthritis patients [33].

ii) Elevated level detection of antibodies in the serum & or synovial fluid of patients with Rheumatoid Arthritis [34].

iii) Significant improvements in RA disease parameters following β cell depletion therapy, e.g. with the use of anti CD-20 antibodies [35].

Role of Humoral autoimmunity (HLA) genes in Rheumatic Arthritis

It has been examined that the gene plays an important role in the development of rheumatoid arthritis mainly through family, twin & molecular analytical studies. At a time familial distribution of Rheumatic Arthritis among first degree relatives [36] & twins [37] indicates that Rheumatic arthritis runs in some families, basically supporting the genetic concept distribution, but at the same time an arguing against the suggestion that Rheumatic Arthritis could be considered as a purely genetic disorder. However, in two separate genome wide screening with affected sib it has been shown that Humoral Autoimmunity (HLA) Haplotype largest genetic contribution in Rheumatic Arthritis [38,39]. About 3 decades ago, HLA-DR4, first genetic marker among other class II molecules was found to be significantly linked with Rheumatoid Arthritis Susceptibility[40].

Later it has been shown that association or dissociation various other HLA DRB 1 alleles with Rheumatoid Arthritis[41].

Despite difference in the distribution of Humoral Autoimmunity genes among various ethnic groups, it has been reported that more than 95% of the patients at least one of the RA linked HLA DR molecules [42], which contain the “SE” amino acid sequence. Further Rheumatic Arthritis associated HLA-DRB1 alleles have also been reported to have a great impact on the disease severity & extra articular manifestation in patients with Rheumatic arthritis [43].

Immunological & molecular links between Rheumatic Arthritis & Proteus

During the last 3 decades, a lot of literature published on the link between Proteus microbes & Rheumatic Arthritis in reviewed journals, some of evidence & studies were carried out by various independent groups worldwide which have been listed in below in following Table.

Table I. Chronologically listed evidence of microbiological, molecular and immunological links between Proteus microbes and rheumatoid arthritis

S.No.	Reference	Basic results	Methods used
1	Chandler et al. (1971)	Elevated antibodies to Proteus OXK and herpes virus, but not to 22 other microbial agents in RA patient then compared HCs.	Direct agglutination assay
2	Ebringer et al. (1985)	Elevated antibodies to P. mirabilis but not Klebsiella microbes in patients with RA when compared to AS patients and HCs.	Indirect agglutination assay
3	Abuljadayel et al. (1988)	Elevated anti-Proteus antibodies in RA patients compared to HCs.	IIF
4	Rogers et al. (1988)	Elevated levels of anti-Proteus antibodies in RA patients compared to other disease or healthy controls.	ELISA
5	Nasonova et al. (1989)	Increased anti-Proteus antibodies the majority of Russian RA patients when compared to corresponding disease or healthy controls.	ELISA
6	Wilson et al. (1990)	Increased isolation of P. mirabilis from urine of RA patients when compared to patients with OA or to HCs.	CLED (Oxoid Ltd) growth and API20E (bioMerieux, Inc) identification methods
7	Deighton et al. (1992b)	Absence of positive correlations between elevated antibodies to P. mirabilis and antibodies against 4 viruses and 8 auto-antigens in patients with RA then compared to HCs	IIF
8	Ebringer et al. (1992)	Molecular homology between Proteus haemolysins and HLA-DR4/1 antigens.	SwissProt and GenBank database search
9	Ebringer et al. (1993)	Increased isolation rate of P. mirabilis from urine of female more than male patients with RA and in RA patients as a whole when compared to healthy volunteers.	CLED growth and API20E (bioMerieux, Inc) Identification methods
10	Fielder et al. (1995)	Elevated antibodies to P. mirabilis but not to E. coli or S. Typhi bacteria in French patients with RA then compared to corresponding HCs.	ELISA and IIF

11	Subair et al. (1995)	Elevated antibodies to <i>P. mirabilis</i> but not to <i>E. coli</i> or other normal bowel microbial inhabitants in Bermudian patients with RA when compared to corresponding HCs.	ELISA and IIF
12	Wilson et al. (1995)	Molecular similarities between Proteus urease and collagen type XI antigens. Elevated antibodies to <i>Proteus haemolysin</i> and urease as well as HLA-DR4/1 and collagen antigenic peptides.	SwissProt and GenBank database search and ELISA
13	Tiwana et al. (1996)	Elevated antibodies to <i>Proteus</i> , but not to <i>Serratia</i> , <i>Escherichia</i> and <i>Pseudomonas</i> bacteria in RA patients when compared to HCs.	ELISA
14	Wanchu et al. (1997)	Elevated antibodies to <i>P. mirabilis</i> but not to <i>S. typhi</i> in Indian patients with RA when compared to OA patients and to HCs.	Tube agglutination
15	Wilson et al. (1997)	A positive correlation between high serum anti- <i>Proteus</i> antibody levels and urine <i>Proteus</i> isolation rates in patients with RA.	ELISA and API20E methods
16	Blankenberg-Sprengels et al. (1998)	Elevated anti- <i>Proteus</i> , but not anti- <i>Klebsiella</i> antibodies in Dutch RA patients when compared to patients with AS or to HCs.	IIF
17	Tiwana et al. (1999)	In vitro and in vivo immunological cross-reactivities between antibodies against <i>P. mirabilis</i> and self-antigenic peptide molecules.	ELISA and peptide finding dilution assay
18	Rashid et al. (1999)	Elevated antibodies to <i>P. mirabilis</i> in Spanish and Norwegian patients with RA when compared to corresponding HCs.	IIF
19	Senior et al. (1999)	<i>Proteus</i> bacteriuria and elevated levels of anti- <i>Proteus</i> antibodies in urine and serum of patients with RA when compared to HCs.	ELISA and Immunoblot
20	Ushakova et al. (2000)	Elevated IgM and IgG antibodies to <i>P. mirabilis</i> in Russian patients with RA when compared to HCs.	ELISA
21	Wilson et al. (2003)	In vitro immunological cytotoxicity reaction occurring between anti- <i>Proteus</i> and anti-	ELISA and sheep red cell haemolytic assays

		HLA-DRB1 antibodies with the corresponding crossreactive peptide molecules	
22	Rashid et al. (2004)	Finish and Japanese patients with RA had elevated antibodies against whole and synthetic peptide antigenic preparations from <i>P. mirabilis</i> but not those from <i>E. coli</i> and <i>S. marcescens</i> when compared to corresponding HCs.	ELISA and IIF
23	Newkirk et al. (2005)	Elevated IgM and IgA antibodies to <i>P. mirabilis</i> and IgA antibodies to <i>E. coli</i> but not to 6 other bacterial and viral agents in rheumatoid factorpositive RA patients when compared with other rheumatic diseases.	ELISA

ELISA = Enzyme linked immunosorbent assay; HCs = Healthy controls; IIF = Indirect immunofluorescence; RA = Rheumatoid arthritis; AS = Ankylosing spondylitis; OA = Osteoarthritis; CLED = Cystine lactose-electrolyte deficient

Proteus Urinary Tract Infection & Rheumatoid Arthritis

Various microbiological & immunological data results support the Proposition there is a link between Rheumatoid Arthritis & Urinary tract infection (UTI) mainly caused by *Proteus*.

Various patients with Rheumatoid Arthritis were reported to have a higher frequency of recurrent UTI's [67, 68].

Urine sample examined from Rheumatoid Arthritis patients yields higher isolation rates of *Proteus Mirabilis* microbes than patients with osteoarthritis or healthy control [51].

Rheumatoid Arthritis Patients higher level of antibodies against 'Proteus' in their urine & shows significant correlation between serum anti-proteus antibodies & *Proteus* urinary isolation rates in rheumatoid arthritis patients when compared to healthy subjects [58]. Rheumatoid arthritis receiving a vegetarian diet had a drop in the levels of antibodies against *Proteus Mirabilis* but *E. coli* when compared to omnivores [69].

The specific antimicrobial effect of this dietary treatment might have been exerted through the actions of lignans & phytoestrogen metabolites [70] which are known to possess antibacterial activity *In vitro* [71].

Females are more susceptible to develop UTI's than males were 60% women have been reported to develop at least one episode of UTI's in their lifetime [72]. Many of these women might have recurrent infection by *Proteus* species which is found to increase with age [73]

Evidence showing Direct & Indirect links between *Proteus* Urinary tract infection (UTI's) & rheumatoid arthritis (RA)

Direct Evidence:

1. *Proteus mirabilis* bacteria were isolated more frequently in patient with RA than those with other disease & healthy controls [49,62].
2. A positive correlation has been detected between anti – *proteus* antibodies & the rate of isolation of these microbes from the urine of rheumatoid arthritis patients when compared to healthy subject [58].
3. Rheumatoid arthritis patients having vegetarian diet are controlled by the level of anti-*proteus* antibodies than omnivores [69].
4. Increased levels of anti-*proteus* antibodies were observed in the sera of Rheumatoid arthritis patients coming from 15 different countries [74].

Indirect Evidence:

1. Patients with severe Rheumatic arthritis had a higher frequency of recurrent Urinary Tract Infection's (UTI's) [67].
2. Women are more liable to develop recurrent UTI's [75].
3. *Proteus* bacteria, which are urease – positive account for 15% of UTI's & affect the upper urinary tract, especially Kidney, whilst *E.coli*, another urogenic but urease – negative bacteria, account for the majority of UTI's & mainly involve bladder [76].

4. Patients with recurrent UTI's are more likely to respond to high daily intake of Cranberry Juice [77] which is still needed to be investigated about the benefits of this in Rheumatoid arthritis patients in a prospective controlled study.

5. Neoplasia (Cancers)

The role of solar short wave ultraviolet B (UVB) irradiance & Vitamin D in reducing the risk of many types of cancer[78-87] is shown by strong ecological & observation evidence. Most of the ecological or observational studies are based on either summer [80] or annual average [86] solar short wave ultraviolet B doses.

Vitamin D

Vitamin D seems to be effective in beating cancer in the latter stages. Most of the study like one shows that annual average solar short wave ultraviolet B was much more strongly inversely correlated with cancer mortality rates than incidence rates [86]. Another recent randomized prospective double blind placebo controlled study that found a 77% reduction in all cancer mortality rates between the ends of the first & fourth years [81]. Another recent study, based on single serum calcidiol measurement up to 12 years prior to death by cancer found significant correlation for breast & colorectal cancer but not all cancer mortality [88]. The mechanism whereby Vit D reduces the risk of cancer are generally well Known [89,90].

There are several recent studies that are not yet in agreement with the ultraviolet B /Vitamin D/ cancer theory.

An inverse correlation between calcidiol levels & cancer incidence couldn't be found in calcidiol based studies from stored sera prior to detection of cancer. A study in Nordic countries found both lower & higher than average than average calcidiol levels correlated with increased risk of prostate cancer [91] stored calcidiol levels in finish smokers have direct correlation with the risk of pancreatic cancer [92]. A study in Linxian, China found serum calcidiol directly correlated with risk of esophageal cancer [93].

The cause of pancreatic cancer is in opposition to many other studies based on ecological studies with respect to indices for solar ultraviolet B& oral intake [80,86,94, 95]. It has been proposed that the finding regarding esophageal cancer in China was due to confounding from immunosuppression by solar UV, thereby increasing the risk of esophageal cancer from

human papillomavirus (96; W.B. Grant, unpublished). An oral source of vitamin D is more important than solar short wave ultraviolet B irradiance in Nordic countries. Therefore, milk is prepared with Vitamin D in Sweden & dairy products are correlated with prostate cancer risk in Sweden [97] & pancreatic cancer in the sun Francisco Bay Area [98] while these explanations are conceivable, confirmation will await further evaluation.

These are several Problems associated with using stored sera to investigate the role of vitamin D in reducing the risk of cancer. One is regarded esophageal cancer in China, which was due to confounding from immune suppression by solar UV, thereby increasing the risk of esophageal cancer from human papillomavirus (96; W.B. Grant, unpublished). Another is the measurements of no. of years that are made prior to diagnosis of or death from cancer. Since, vitamin D seems to be much more effective in fighting cancer near the time of detection [81, 86, 99,100] alittle relevance to outcomes may appear in stored sera from many years prior to cancer. In addition, the measurements are generally one –time determination & do not consider changes in vitamin D intake & production over a period of many years. On the other hand, the ecological approach is based on solar short wave ultraviolet B over many years with the possible confounding factor of migration [86]. Another approach that is based on integrated lifetime solar short wave ultraviolet B (UVB) irradiance, the use incidence of Nonmelanoma Skin Cancer (NMSC), approach tested in a meta analysis of cases of second solid tumor after development of NMSC[101]. In order to successfully approach test, it was important to adjust relative risk by the effect of smoking in each study population by using lung cancer incidence rates. Non melanoma skin cancer (NMSC) mortality rate over a 15 year period in continental Spanish provinces were used in another ecological study [102] in which it was reported that Non melanoma skin cancer (NMSC) mortality rates were significantly inversely correlated with 17 types of cancer. Recently, it was pointed that it is not a good index to use. Since the number of nomelanoma skin cancer deaths was small. From the multiple linear regression analysis, it has been analyzed that a total of 15 types of cancer had either latitude or non-melanoma skin cancer as a significant factor. Bladder & Uterine corpus are now removed from the list of short wave ultraviolet B (UVB)/ Vitamin D sensitive cancers in Spain from this study.

Most recently, a linkage study in sunny countries found that non melanoma skin cancer was correlated with reduced risk of solid tumors other than lip or skin cancer [103,104] & a study

in the Netherlands found that diagnosis of skin cancer was correlated with reduced risk of prostate cancer [105].

Thus, this stronger measure lifetime short wave ultraviolet B irradiance is very often found inversely correlated with many types of cancer. Although the causes of cancers are associated with factors related to carcinogens, smoking, alcohol, and dietary factor [106,107] including viral infection.

Cervical cancer is one of this [108], Hodgkin's lymphoma [109], nasopharyngeal cancer [110]. Similarly, viral infection is a risk factor for several are a risk factor for several other cancers, which are not limited to anal cancer [111], bladder cancer [112-115], esophageal cancer, hepatocellular carcinoma [116], oral cancer [117] & prostate cancer [118-121].

Prostate cancer

On hypothetically based data solar short ultraviolet B (UVB) irradiance & vitamin D intake shows effectiveness as a risk reduction factor in one of first cancer i.e Prostate cancer [122]. On geographical variation, the mortality rate due to prostate cancer in US is different from that of many of the other cancers for which short ultraviolet B & vitamin D are risk reduction factors. The prostate cancer mortality rate is more closely tied to a symmetrical latitudinal pattern, whereas other cancer, as breast cancer & colon cancer have asymmetric variation, highest in the northeast & lowest in southwest [123]. Schwartz [124] recognized the prostate cancer mortality rate in the United State have a geographic variation that is similar to that for Multiple Sclerosis. Genital bacterial & viral infection is more common in youth & early adulthood [125], higher level of solar shortwave ultraviolet B exposure & youth are significantly correlated with the reduced risk of prostate cancer [87]. An important risk factor for prostate cancer [126,127] is a viral infection which gives rise to inflammation [136]. The effect of Vitamin D reduces because prostate cells have reduced ability to convert calcidiol to calcitriol due to decreased activity of the 1α – hydroxylase enzyme as the cells turn cancerous [128,129].

Bladder, gastric, prostate, testicular, thyroid cancer & Hodgkin's lymphoma are cancers having a significant correlation with either latitude or temperature. Many of the cancers such as breast cancer [130,131], colon & ovarian [132] cancer do not be viral infection as an important risk factor exacerbated by solar UV & immunosuppression except one i.e. various associated with colon cancer after kidney transplant [133].

6. Proposal of a new therapeutic strategy

At present rheumatoid arthritis patients are being treated with various therapeutic strategies involving the use of anti-inflammatory, immunosuppressive & biological agents as well as non-medical treatment metabolites [134].

The current medical treatments are expensive [135] & cause side effect, although they have a promising beneficial effect, particularly in easing or even halting the disease progress especially those involving anti tumor necrosis factor therapies [136].

Based on existing evidence for involving Proteus bacteria in the pathogenesis of Rheumatoid arthritis, it is logical to propose new therapeutic modality in the management of Rheumatoid arthritis, which could be implemented in conjugation with other currently used treatment.

The new treatment includes anti-proteus measure involving the use of Proteus sensitive antibiotics with vegetarian diet manipulation [69] with daily high intake of water & fruit juices containing fructose such as Cranberry juice [137].

Vaccine derived mainly from Proteus antigenic molecules that do not contain the cross-reactive epitopes could be possible to develop in order to prevent susceptible individuals of acquiring Proteus UTI's & decrease the possibilities of developing Rheumatoid arthritis or at least limit further damages in those with established disease.

7. New Drug for the treatment of Rheumatoid arthritis

Drug	Primary Action	Route of Administration	Usual Dose	Half-life
Leflunomide	Inhibits pyrimidine Synthesis	Oral	Loading dose of 100 mg daily for 3 days, then 20 mg daily	2 Wk
Etanercept	Binds TNFa and TNFb	Subcutaneous Injection	25 mg twice/wk or 50 mg once/wk	4 Days
Adalimumab	Human anti-TNFa Antibody	Subcutaneous Injection	40 mg every second wk	2 Wk
Infliximab	Chimeric anti-TNFa Antibody	Intravenous Infusion	3 mg/kg of body weight at 0, 2, and 6 wk, then every 8 week For incomplete response, maintenance dose may be gradually increased to a maximum of 10 mg/kg	9 Days
Anakinra	Interleukin-1-receptor Antagonist	Subcutaneous Injection	100 mg daily	6 Hr

8. Pregnancy & autoimmune rheumatic disease

Pregnancy is a state of high concentration of sex hormones & cross communication between mother & fetus. Throughout this stage, many of the changes like hormonal, biochemical & immunological equilibrium occur. However, tolerance to semi-allogeneic fetus at all stages is maintained by a supportive immunological milieu [138].

Clinical symptoms of the autoimmune rheumatic diseases vary related to the pathogenesis. Some improve spontaneously during gestation; others remain active or even flare. Likewise, pregnancy outcomes are different depending on diseases extent & severity.

TABLE III Interaction of pregnancy and some CTDs or vasculitis

Disease	Effect of pregnancy on disease	Risk of maternal complication in pregnancy	Risk for pregnancy complications	Risk for fetus /Neonates
neonate RA	Improvement in 48_75%	No	Moderate increase	Very rare
SLE	Flare in 50% of cases	Most frequent: haematological, and renal complications	Hypertension, pre-eclampsia, prematurity	Fetal loss, intrauterine growth restriction, low birthweight, neonatal lupus
APS	Aggravation	Thrombosis	Pre-eclampsia, prematurity, HELLP syndrome	Fetal loss, intrauterine growth restriction, low birthweight
SSc	No major effect on disease activity	Not more frequent than outside	Prematurity	Reduced birth weight in premature infants
Takayasu Arteritis	Unchanged in 72%, improvement in 20%	Progression of renal insufficiency, congestive heart failure	Hypertension in 30-44% Pre-eclampsia in 12-16%	Only at severe maternal disease, otherwise 85% good neonatal Outcome
ANCA-positive Vasculitis	Data insufficient to discern a particular effect	Renal and pulmonary Disease	Pre-eclampsia, prematurity	Fetal loss, intrauterine growth restriction, low birthweight

HELLP: haemolysis, elevated liver enzymes, low platelet.

Rheumatoid Arthritis & Antiphospholipid Syndrome (RA & AS)

Retrospective & some prospective studies have shown that rheumatoid arthritis improves during pregnancy & burst after delivery.

The largest prospective study from the Netherlands evaluating the effect of Pregnancy on arthritis & the impact of rheumatoid arthritis on pregnancy includes 200 women at present [139], 48% of the rheumatoid arthritis patient improved during pregnancy, according to the 28 joint DAS (DAS -28) derived EULAR response criteria, whereas 41% flared after delivery according to revised EULAR response criteria [139].

The disease activity of rheumatoid arthritis during pregnancy, neither improvement nor the post-partum flare was associated with changes in levels of anti-citrullinated protein antibodies (ACPAs) or RF [140]. However, women negative for ACPA or RF were more likely to improve during pregnancy [140].

Higher disease activity during pregnancy was associated with lower birth weight. Gestational age at delivery of patient using prednisone was significantly shorter & their delivery more often premature. The pregnancy induced amelioration of rheumatoid arthritis provides a way into pathogenic mechanism.

Micromerism (MC) refers to a small number of cells (or DNA) possessed by one individual that originated in a genetically different individual. Pregnancy has both short term & long term immunological effect. Higher levels of fetal Micromerism (Mc) were found in the circulation of women with rheumatoid arthritis who improved during pregnancy compared with those who did not [141].

Pregnancy also leaves a heritage for the long term as it is now known that fetal Micromerism persists in the mother & maternal Micromerism in her offspring. Women with rheumatoid arthritis who were themselves negative for HLA alleles associated with rheumatoid arthritis risk were recently reported to harbor Micromerism with rheumatoid arthritis risk allele's significantly more often healthy women [142]. Thus, Micromerism could contribute to both health & disease.

Those factors influencing disease activity & immunological mechanism of fetal-maternal tolerance are $CD_4^+ CD25^+FOXP 3^+$. Tregs (The regulatory T cells). Tregs are formerly known as suppressor T cells that supports the maternal tolerance towards the fetus. In healthy women, the no. of circulating Tregs increases during pregnancy & decline postpartum. The same expansion found in with rheumatoid arthritis & antiphospholipid syndrome patient [143,144]. However, unlike in healthy women, Tregs of rheumatoid arthritis &

antiphospholipid syndrome patients are unable to suppress effected the pro-inflammatory cytokine response of T – effector cells [144].

In rheumatoid arthritis, pregnancy restores suppressor T cell function creates an anti – inflammatory cytokine milieu in the third trimester at the time of maximal improvement of rheumatic arthritis disease activity [143]. In contrast to rheumatoid arthritis, pregnancy does not alter the disease activity in Antiphospholipid syndrome. This was reflected by a defective Treg function with impaired capacity to suppress pro-inflammatory cytokines [144]. Thus, the different clinical response of rheumatoid arthritis & antiphospholipid syndrome in pregnancy corresponded to different response at the cellular level.

Systemic Lupus Erythematosus (SLE)

In contrast to rheumatoid arthritis, systemic lupus erythematosus often remains active or even flares during pregnancy. A clear difference is observed in hormonal & cytokine levels in systemic lupus erythromatous Vs control pregnancies [145]. An increase in renal burst in pregnant systemic lupus erythromatous patient data have been shown from the Hopkins Lupus pregnancy cohort [146]. However, a change in the renal disease activity& deterioration in renal function in pregnant patients has been found from a Canadian prospective study which is similar to those which occur in non –pregnant patients with LN [147]. Other studies have shown that Systemic Lupus Erythematosus flares are not more severe in pregnancy than in the non-pregnant state [148].

The combination of high clinical activity & abnormal serology (complement or anti- ds DNA is most predictive of a poor obstetric outcome [146]. When there is proteinuria, APL, thrombocytopenia or hypertension at the first pregnancy visit, pregnancy loss is increased [146].

One of the concerning therapy in pregnancy is HCQ therapy, as the treated pregnancy have fewer preterm births, &less severe clinical activity [149]. Prednisone at high concentration, is associated with more diabetes, hypertension & pre- eclapsia.

The PROMISSE(Predictors of pregnancy outcomes: biomarkers in antiphospholipid syndrome & systemic lupus Erythematosus study is an ongoing prospective observational study to identify markers that predict poor pregnancy outcomes i.e. fetal growth restriction,

preeclampsia, fetal on mental death. Complement activation & angiogenic factors are the focus center point in predicting poor outcome [150].

Neonatal Lupus Syndromes:

Neonatal lupus syndromes are induced by Transplacental transfer of Ro/SSA antibodies, either as a typical skin rash that resolves spontaneously within 6 months after birth or a congenital heart block (CHB) in the child. Atrioventricular (AV) block is defined as congenital if diagnosed in utero, at birth or within the neonatal period (0-27 days after birth).

The most common presentation is unexpected advanced AV block in the fetus of a healthy asymptomatic mother (85% of cases) [151]. It is difficult to differentiate between complete & incomplete block in utero. The risk of delivering a child with complete CHB for anti – Ro/SSA positive mothers is 1-2% [151]. The risk of recurrence is 15-20% unfortunately high dose IVIGs are not effective in reducing this risk [152].

Other minor Electrocardiogram (ECG) abnormalities may be present in infants born by anti-Ro/SSA positive mothers like PQ prolongation, sinus bradycardia. Anti-Ro/SSA antibodies do not negatively affect other pregnancy outcomes [151].

Anti-phospholipid Syndrome

aPLs are associated with recurrent pregnancy losses. Different pathogenic mechanisms mediated by aPLs have been described, such as:

- i) Placental thrombotic events;
- ii) Placental inflammatory events following local complement (C') activation;
- iii) Direct aPL effect on trophoblast cells, inducing defective placentation.

Placental thrombosis & recurrent miscarriage were no more frequent in patient with APs than in patient with APL negative. There were no specific placental lesions or patterns of abnormalities characteristic of the primary APS (PAPS) [153].

In a prospective study, histological & immune histochemistry analysis of term placentas or abortive materials was carried out in 14 pregnancies of women affected by APS & compared with five matched controls [154]. No specific histological pattern or widespread

inflammation was found. Although complement activation was detected for the first time in APS placental both in abortive specimens & in placentas at term, there was no relationship with therapy or pregnancy outcome. These results suggest that complement activation may contribute to placental damage.

The poor pregnancy outcome in patient with APS has been changed to nearly 80% of live birth by therapy with anti-aggregation (low dose aspirin) alone or in combination with anticoagulation low molecular weight heparin). However, 20% of pregnancies still experience poor outcome despite conventional treatment. After failure of conventional therapy, various treatments have been suggested by ranging from increasing the dose of low molecular weight heparin or adding either steroid HCQ or IVIG [155].

Recently, the antiphospholipid European forum promoted a multicenter project for collecting cases of pregnancy loss despite anti-aggregating and anticoagulation treatment women with Antiphospholipid & matched controls [156]. Preliminary results showed that women with unsuccessful pregnancies were more likely to be those with SLE, or with a history of thrombosis or thrombocytopenia.

A severe complication in both Systemic Lupus Erythematous & Antiphospholipid (APS) is the increased risk of preeclampsia triggered by placental dysfunction caused by maternal endothelial cell dysfunction. Both genetic polymorphisms & dysregulation of angiogenic factors [157] & a variety of other factors are involved in pathogenesis of preeclampsia. It has been hypothesized that soluble Fms-like tyrosine kinase (sFlt-1) increment in circulation contributes to the endothelial dysfunction, hypertension & proteinuria of preeclampsia. Finally, elevated sFlt-1 levels have been detected in systemic lupus erythematous pregnancies at risk for pre-eclampsia [158].

A recent study showed that cell-free, fetal nucleic acids (DNA & mRNA) are released by the placental trophoblast & are elevated in cases with manifest pre-eclampsia, which is correlated with disease severity & were higher at early onset than in late-onset pre-eclampsia [159]. Furthermore, cellfree DNA levels were found to be elevated early in pregnancy that subsequently developed preeclampsia but not in those with normal pregnancy outcomes.

Systemic Sclerosis (SSc)

In the past, pregnancy SSc patients were thought to be at high risk for poor fetal & maternal outcomes. But recently, Italian study considered the largest up to now, 17 centers prospectively followed 70 pregnancies in 62 women with SSc.

Pregnancy losses occurred in 4% of SSc women Vs 15% of Systemic lupus erythromatous women, with prematurity as the most adverse outcome in SSc; pre-eclampsia & hypertension occurred most frequently in Systemic Lupus Erythromatous (SLE).

A pregnancy outcome similar limited & diffuses SSc & was not correlated with the disease activity. SSc skin involvement remained stable at 69% of women, RP improved in 40 %; oesophageal reflux worsens in 24%; spirometry remained stable at 72% & echocardiography was in stable in 98%. No renal crisis except pulmonary hypertension in one is observed. From the study confirms that women with SSc can have uncomplicated, successful pregnancies [160].

Vasculitis

Improvement in diagnosis of primary systemic vasculitides has led to an earlier detection & treatment with the consequent improvement of survival rate as well as quality of life. For this reason, reproduction is becoming an important issue in patients with systemic vasculitides. Data on pregnancy in patients with systemic vasculitides are scarce due to their low incidence, low female male ratio or their frequent disease (onset after childbearing age).

Maternal & fetal outcomes has been satisfactory in most patients with Takayasu arteritis, WG & Churg- Strauss Syndrome when the disease activity was well controlled [161].

Patients with active vasculitis at conception or disease onset during pregnancy are at increased risk for adverse pregnancy outcomes. The severity of the initial manifestations of vasculitis does not predict the activity of the disease during pregnancy.

Preconceptional Counselling of high risk - Pregnancies

Coordinate medical care is essential to maximize the chance of successful to maximize the chance of successful pregnancy outcomes in women with vasculitis or CTD [162]. The

requirements for good pregnancy outcomes are optimum disease control & preferably remission or low disease activity before pregnancy.

Previous complicated pregnancies, renal disease, irreversible organ damage anti- Ro/SSA & aPL treatment with high doses of glucocorticoids increase the risk of complication. Pregnancy is contraindicated in women with symptomatic pulmonary hypertension, heart failure, severe restrictive pulmonary disease, severe chronic renal failure, recent high disease activity & recent arterial thrombosis.

Fertility

Infertility affects 10-15% of all couples, & is higher in male & female patients with rheumatic disease [164]. The world health organization (WHO) has published the normal values of sperm parameter in 1992 & 1999 & for its morphology in 1998 by Kruger. However, nearly all reference values (especially morphology) have been questioned. A Swiss study of proven fertile men who has a pregnant partner at the time of study inclusion showed high variability of several sperm parameters, especially morphology [163].

Similar results were found in young swiss recruits [165]. This diagnosis of male infertility can be made because of a single abnormal parameter since there are wide ranges for most sperm parameters. A combination of several semen criteria is more predictive.

A Brazilian study revealed impaired testicular & sexual function in 35 male Systemic lupus erythematous patients [166]. SLE patients had a lower median testicular volume in both testes, total sperm count & total motile sperm count compared with 35 healthy controls & also compared with patient without this treatment [166].

Almost a quarter of SLE patients had Sertoli cell dysfunction, according to low serum inhibin B, & the serum level was lower in SLE.

Further evaluation of the 26 SLE patients with normal inhibin B & Follicle Stimulating Hormone(FSH) levels revealed that median of inhibin B: FSH ratio was lower in SLE patients with oligozoospermia compared with normozoospermia [167]. Hence, the frequencies of sexual /erectile dysfunction were significantly higher in SLE Vs controls [167].

Molecular mimicry as a plausible aetiopathogenetic mechanism

Molecular & immunological interrelation between the triggering aetiological factor, namely *Proteus mirabilis* antigens & targeted synovial tissue structures expressing HLA molecules that contain “SE” amino acid motif & collagen Type XI, in Rheumatoid arthritis could be explained by the molecular mimicry or cross-reactivity mechanism [168]. Titration of high antibody against *Proteus* haemolysin & ureas antigens in patients with active Rheumatoid arthritis could bind to cross-reactive self antigens & consequently result in production of various inflammatory & immunological damaging mediators based on the mechanism of antibody mediated cytotoxicity reactions (Figure 1). The release of self antigenic particles and autoantibody production could be the result of synovial & other joint structure damage. Anti-proteus cross-reactive antibodies which might result from recurrent albeit subclinical UTI's together with high levels of secondary autoantibodies will bind to Rheumatoid arthritis targeted antigens in the synovial tissues. These immunological reactions could coincide with the initiation of clinical & laboratory exacerbation & further pathological damages.

9. Clinical Use

Treatment of rheumatoid arthritis is typically initiated by non-steroidal anti-inflammatory drugs & simple analgesics to relieve pain & stiffness. Disease-Modifying Antirheumatic Drugs (DMARDs) which improve symptoms & reduce erosive damage are initiated as early as possible.

The most commonly used DMARDs include;

- Methotrexate
- Sulfasalazine
- Leflunomide (Arava, Aventis)
- Hydroxychloroquine (Plaquenil, Sterling winthrop) &
- Cyclosporine (Sandimmune, Novartis)

Among these, Methotrexate is, mostly used. Synergistics can be seen in combination of two or more conventional DMARDs [169] steroids (intra-articular, intramuscular) or oral are often used to manage disease flares.

Tumor Necrosis Factor(TNF) inhibitors are usually given to patients with active rheumatoid arthritis where satisfactory response has not been achieved with one or more conventional DMARDs such as Methotrexate. It depends on constitute of active rheumatoid arthritis[170].

One or six or more tendons & three or more swollen joints together with either an erythrocyte sedimentation rate greater than 30 mm per hour or at least 45 minutes of morning stiffness. Another defines as a disease activity score of more than 5.1 (range of scores 0 to 10) with higher scores indicating more active disease), although some experts have expressed concern about the inherent variability of these scores [171].

The concept of treatment failure with DMARDs is also inadequately defined. Many rheumatologist use clinical opinion alone while others rely on predetermined definitions. In the United kingdom, such failure is defined as “failure to respond to or tolerate adequate therapeutic trials of at least two standard DMARDs” with an adequate therapeutic trial involving at least six months of therapy unless limited by significant toxic effects [172]. Although this definition is not universally strict.

Prior to the initiation of Tumor Necrosis Factor (TNF) inhibitor therapy, patients should screen for latent tuberculosis & antituberculosis prophylaxis should be considered for patients at risk [173]. To prevent contraindications to treatment, patients should also be evaluated for evidence of other pre existing infections. Since TNF inhibitors should be probably avoided in the presence of certain chronic infections such as with hepatitis B. Practitioners should exercise extreme caution & expert’s advice before prescribing TNF inhibitor for a patient with a coexisting infection.

Live vaccination is contraindicated in patient receiving TNF inhibitors as well as those taking others DMARDs such as Methotrexate, where an alternative non –live vaccine is not available, consideration should be given to vaccination before starting TNF inhibitor therapy.

There are no clinical trials comparing one TNF inhibitor with another. The choice of agent, therefore, depends on other factors, including patients’ convenient access to treatment & patients’ preferences.

Infliximab requires an infusion intravenously every four to eight weeks performed by a healthcare professional. The usual dose is 3 mg per kilogram of body weight; some patients require higher doses. Infliximab is given with methotrexate to prevent the information of

human antichimaeric antibody (HACA). Since HACA increases the likelihood of infusion reactions & accelerates infliximab clearance. Etanercept and Adalimumab are self administered by subcutaneous injection. Etanercept is given at a dose of 25 mg twice weekly or 50 mg weekly & adalimumab is self administered by subcutaneous injection. Although concomitant Methotrexate therapy is not essential with the use of these agents, combination therapy is more effective & is now recommended for adalimumab, unless there are contraindications.

As noted, TNF inhibitors have been studied primarily in comparison with or in addition to methotrexate. There are no trial data on the use of TNF inhibitors with other conventional DMARD's but observational studies suggest that this is practically & effective when methotrexate cannot be used.

The combination of TNF inhibitors with new biologic agents such as anakinra (Antril, Synergen) (an interleukin -1 receptor antagonist) & abatacept (Orencia, Bristol –Myers Squibb) (a T-cell costimulation inhibitors) is not recommended since studies have shown an increased risk of serious infection.

DMARD's such as methotrexate require routine safety monitoring to detect blood & liver toxicity, monitoring required for the use of TNF inhibitors except a regular assessment for clinical evidence of serious side effects such as infection & should be warned to contact a physician immediately in the event of fever or other symptoms of infections.

TNF inhibitors are expensive, as data supplied by the manufacturer suggest that TNF inhibition is cost effective, according to commonly applied threshold of \$ 50,000 per quality adjusted life year gained [174,175]. However, reports commissioned by regulators & reports based on independent data both suggest that they are substantially less cost effective [176,177]. Hence, the relative expenses of TNF inhibitors make their universal use impractical.

Treatment with TNF inhibitors should be stopped if they are evidence of drug related toxic effect or no evidence of efficacy within 3 to 6 months. The definition of clinical efficacy is also contentious. Our European view suggests that a fall in the score for disease activity of more than 1.2 indicates efficacy. If treatment with one TNF inhibitor is stopped because of inefficacy or an adverse event, there is evidence that an alternative TNF can be effective.

10. Adverse Effect

Injection site reaction with Etanercept & Adalimumab & infusion reaction with Infliximab are the most common minor adverse effect of clinical therapy of Rheumatoid Arthritis [178] while optic neuritis, exacerbations of previously dormant multiple sclerosis, aplastic anemia & interstitial lung disease, lupus syndrome & hepatotoxicity are rare serious adverse effect.

Serious infections are a particular concern [179-181], especially respiratory & skin infection. So TNF inhibitor should be stopped in the presence of severe infection.

Increase in susceptibility to intracellular pathogens, primary tuberculosis & reactivation of prior tuberculosis are specific problems [182,183].

The overall risk of cancer is controversial. The only systemic review, which focused on randomized & controlled trials involving infliximab & adalimumab but not Etanercept, reported a dose related increased risk of cancer [181].

In contrast, rational registries have not yet found an increase in solid cancer after treatment with TNF inhibitors [184,185].

An increase in lymphomas has been reported with all TNF inhibitors [181,186-188] because the preexisting association of lymphomas with severe rheumatoid arthritis & systemic inflammation [189]. The exact contributions of TNF inhibitor therapy are difficult. With these sort of uncertainties, extreme caution is to be considered in the patient with a history of malignant disease or even to avoid them or to warn the patient with the risk.

Serious Adverse Events Associated with TNF Inhibitors.

Evidence	Infections		Cancers		
	Serious Infections	Tuberculosis	All Cancers	Solid Tumors	Lymphoma
Meta-analysis of clinical trials of infliximab and adalimumab ^{181,†}	Patients, 3.6% Controls, 1.7% NNH, 59		Patients, 0.9% Controls, 0.2% NNH, 154		
National registries [‡] United Kingdom ^{180,182}	Infliximab, 5.2/100 PY Etanercept, 5.3/100 PY Adalimumab, 6.3/100 PY		Patients receiving all agents, 0.86/100 PY Controls, 1.42/100 PY		
Sweden ^{183,185,188}		Infliximab or etanercept (relative risk, 4.1)		Patients receiving all agents, 0.9 SIR Controls, 1.1 SIR	Patients receiving all agents, 2.9 SIR Controls, 2.0 SIR
Germany ¹⁷⁹	Infliximab, 6.2/100 PY Etanercept, 6.4/100 PY Controls, 2.3/100 PY				
Other Consensus ¹⁸²	Infliximab, 0.07/100 PY Etanercept, 0.02/100 PY Adalimumab, 0.27/100 PY				
U.S. national databank ^{186,§}					Patients receiving all agents, 2.9 SIR Controls, 1.5 SIR
Comment	Increased risk of serious infections, including tuberculosis, with all agents in all types of study		Increased overall risk of cancer shown in a meta-analysis of clinical trials, but too few cases to differentiate between solid tumors and lymphomas. National registries and U.S. databank shows no increase in overall risk of cancer or solid tumors but an increased risk of lymphoma.		

* NNH denotes number needed to harm, PY patient-years, and SIR standard incidence ratio.

† Control subjects were patients who underwent randomization but did not receive TNF inhibitors.

‡ In the U.K. and German registries, the controls were patients with RA who were treated with disease-modifying antirheumatic drugs. In the Swedish registry, the controls were a cohort with early RA; data on an inpatient RA cohort were also available.

§ Controls were patients with RA who were treated with methotrexate only; data on patients with RA who did not receive methotrexate were also available.

Since infliximab increases mortality when used to treat severe heart failure in patient without arthritis [190]. However, no evidence that TNF inhibitor increases the risk of new onset cardiac failure in patients with rheumatoid arthritis. [191,192].

Patients are usually advised not to conceive while taking TNF inhibitors & also during pregnancy or lactation. No actual adverse events have been described in those pregnancies that have occurred in patients taking TNF inhibitors. [193]

Thus the wider use of TNF antagonist has resulted in reports – largely case reports or small series of patients that links TNF inhibitors use with a wide range of adverse events, including infections, cancer, vasculitis, lupus-like autoimmune disease, multiple sclerosis like demyelinating disorders, liver disease, hematologic abnormalities including aplastic anemia & lymphoma, severe allergy & aseptic meningitis. [194-202]

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