750 Centigray versus 2000 Centigray Total Lymphoid Irradiation In The Treatment Of Intractable Rheumatoid Arthritis

Thesis

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The MD of **Internal Medicine**
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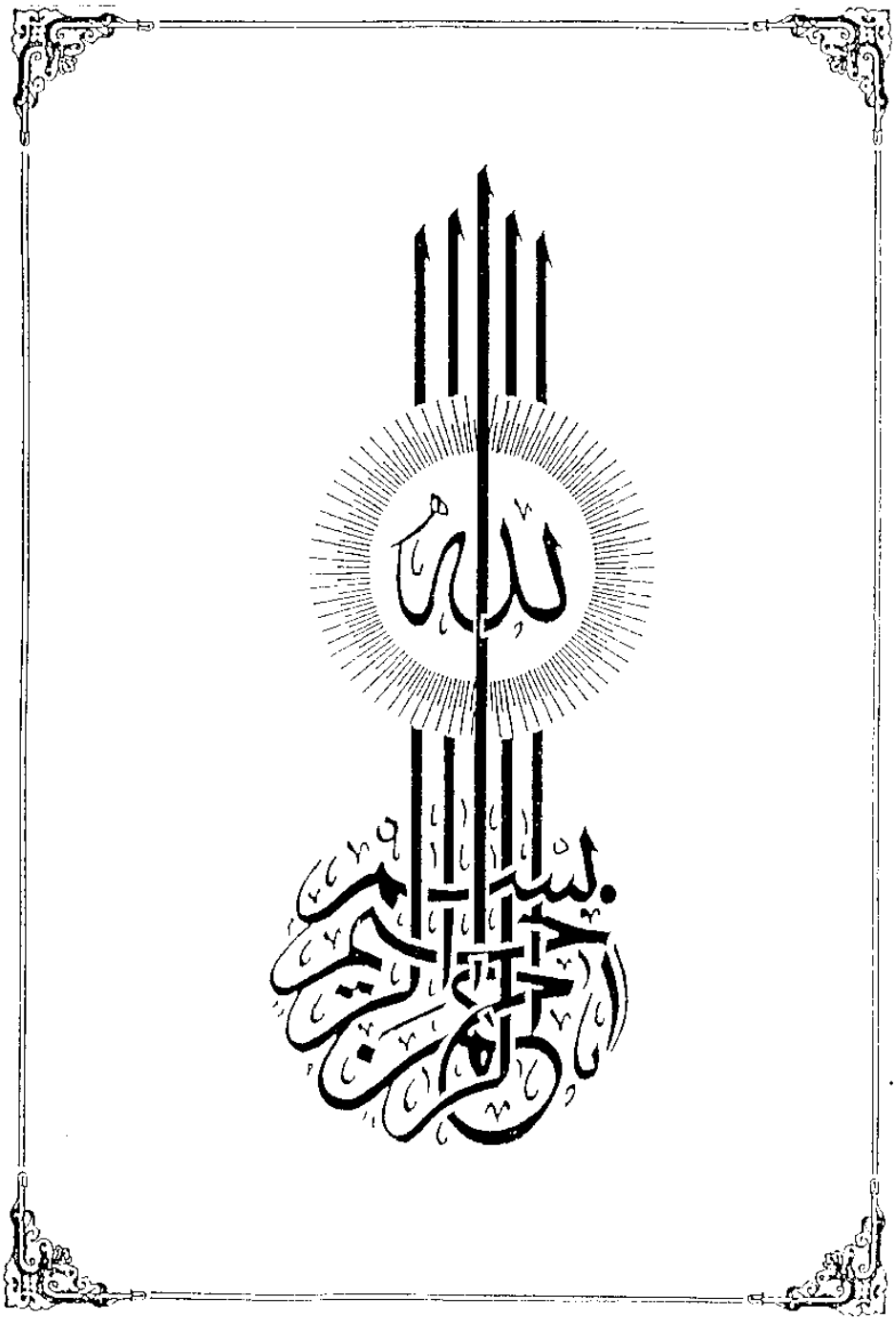

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Dr. Samir Moawad

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Introduction :-

Rheumatoid arthritis (RA) is a common chronic disease. It affects about 1% of the general population worldwide. Rheumatoid arthritis causes great disability and chronic pain, and has a major economic impact upon patients ***(Hellamn and Shearn, 1991).***

A definite trend exists to treat RA more aggressively and earlier in the course of disease. The reasons for this are several. First, it is now appreciated that RA is not a benign disease; there is significant increase in mortality in rheumatoid patients. Second, there is little evidence that current approaches to therapy alter the progression of disease or decrease morbidity ***(Sharp et al, 1991).***

Despite the availability of an ever increasing number of anti-inflammatory and anti-rheumatic drugs, RA remains intractable to conventional treatment in a portion of patients. Not surprisingly, therefore, additional treatment modalities have been tested, most are based on the premise that the chronic inflammatory state in RA is driven by cellular immune responses ***(Hannonen et al., 1993).***

Total lymphoid irradiation (TLI), initially developed to treat Hodgkin's disease, appears to induce a long lasting suppression of immune response regulated by T cells. Total lymphoid irradiation has been shown to be effective in treating RA activity

in a dose of 2000-3000 centigray (cGy). However, serious side effects had been reported ***(Brahn et al., 1984)***. TLI with much lower doses of irradiation (750 cGy) may have as potent an anti-arthritic effect as higher doses of irradiation. If this is truly the case, it may be possible to avoid many of the undesirable side effects.

Aim of the work :-

The aim of this work is to compare 750 cGy TLI with 2000 cGy TLI regarding the therapeutic benefits and side effects of each modality in the treatment of RA intractable to conventional therapies.

Rheumatoid Arthritis
(Introduction)

Rheumatoid arthritis is a common, severe inflammatory disorder, affecting men and women of all ages, with a peak incidence in young adults and premenopausal women. It is a disease of multifactorial origin, including a genetic predisposition, and characterized by immune-driven, chronic inflammation ***(Weyand and Goronzy, 1995)***.

The disease is marked by a variable course, involving exacerbations and remissions of disease activity. Many cases are chronic and progressive, resulting in severe disability and sometimes death ***(Halberg, 1994)***.

Taxonomy :-

The name RA was coined in 1859 by Garrrod. However, compared with today's use of the word, it was a misnomer, since it included not only inflammatory polyarthritis, but also polyarticular osteoarthritis. In 1922, the term covered only inflammatory polyarthritis ***(Parish, 1963)***, and in 1972 and 1987 the seronegative arthritides were excluded from the term ***(Arnett et al., 1988)***. The concept of a disease entity changes continuously, influenced by advances in knowledge and by "splitters" and "lumpers" of syndromes. Many clinicians feel that even the modern classification of RA included more than one disease entity ***(Halberg, 1994).***

Rheumatoid Arthritis
(Etiology & Pathogenesis)

Etiology of rheumatoid arthritis :-

Rheumatoid arthritis is one of a group of conditions, frequently referred to as autoimmune diseases, in which disordered immunologic activity is probably involved. Rheumatoid arthritis can now be appreciated as a process determined by immunogenetics of class II major histocompatibility (MHC) loci, precipitated by unknown antigens and resulting in poorly restrained proliferation of macrophages, T and B lymphocytes and their products. The inflammation that these cells and their gene products evoke leads to proliferation and activation of synovial cells, and these, behaving much as a localized malignancy, invade and destroy articular cartilage, subchondral bone, tendons and ligaments ***(Harris, 1993).***

Rheumatoid arthritis is likely the result of a concerted action of several inherited and non-inherited factors. Although there is a high suspicion that environmental factors are important, proof is missing. Most information has been collected on genetic risk factors. The inheritance pattern for RA is complex, and there is good evidence that HLA genes are involved ***(Weyand and Goronzy, 1995).***

1- Host factors in the development of RA :-

It is becoming apparent that many host influences are major determinants in the development of this disease ***(Weyand and Goronzy, 1992).*** Although immunogenetics may be the most

dominant of these, the most powerful additional factor recognized in the host is the sex of the patients ***(Buyon et al., 1984).***

Sex and pregnancy :-

Rheumatoid arthritis is one of many autoimmune diseases that predominate in females. The ratio of female to male patients (2:1 to 4:1) is significant. Estrogens have multiple effects on T lymphocytes and may inhibit neutrophil activation as well ***(Buyon et al., 1984).***

Still incompletely understood are the mechanisms underlying the effect of pregnancy on RA. ***Hazes, (1991)*** has summarized the epidemiologic data on pregnancy as follows;

- Pregnancy has an ameliorating effect on RA.
- Patients with RA were more often nulliparous before disease onset than controls.
- Perhaps a first pregnancy at a younger age decreases the risk of developing RA.

The possible relationship between alleviation of RA symptoms during the last trimester of pregnancy and immunogenetics may be indicated by the observation that alloantibodies in the maternal circulation are developed during pregnancy against paternal human leukocyte antigen (HLA) antigens ***(Combe et al., 1985).*** Indeed, placenta-eluted gamma globulins have been used in France for 10 years to treat classic, severe, and active RA successfully ***(Moynier et al., 1987).*** Data suggest that these antibodies are directed against class II (DR) HLA ***(Harris, 1993).***

Immunogenetics and other heritable predisposing factors in RA :-

Evidence is accumulating that the structure of class II surface molecules on antigen presenting cells is of equal or even more importance than the nature of the antigen presented to the T lymphocytes at the initiation of immune response in RA ***(Weyand and Goronzy, 1992).***

In the 1970s, Stastny provided evidence that RA was associated with an antigen of the HLA-D locus ***(Stastny, 1976).*** Careful study of the MHC using DNA probes directed against specific α and β chains of the DR loci has revealed "susceptibility cassettes" or shared epitopes on the β chains of DR that predispose to development of RA. The susceptibility epitope is glutamine-leucine-arginine-alanine-alanine or ones with minor substitutions that do not affect polarity of the cassette. This sequence is found in Dw4 and Dw14 (in which RA is more prevalent) and in DR1β chains as well ***(Goronzy et al., 1992)*** (Table I). This sequence motif translates into a pocket in the antigen-binding site of the HLA-DR molecule. This "rheumatoid pocket" accommodates peptide side chains and has distinct binding characteristics ***(Weyand and Goronzy, 1995).***

Another genetic factor that may influence severity, if not susceptibility, to RA is the DQ system. It has been reported that a DR4-associated allele Dqw7 was found to be significantly increased only in patients with severe RA, whereas DR1 was readily increased only in mild RA, often controlled by non

steroidal anti-inflammatory drugs (NSAIDs) ***(McCusker et al., 1991).*** (Table I).

Protective HLA-DR phenotypes can be identified as well. Data suggest that four phenotypes with half or less of the expected frequency of RA are DR1, DR5; DR2; DR2, DR3; and DR3, DR7 ***(Larsen et al., 1989)*** (Table I).

Table (I);

Immunogenetics and rheumatoid arthritis

Increased risk of RA	
	DR4 (Dw4, Dw14)
	DR1
Increased severity of RA	
	DQw7
Decreased risk of RA	
	DR1, DR5
	DR2
	DR2, DR3
	DR3, DR7

(Larsen et al., 1989; McCusker et al., 1991; & Goronzy et al., 1992)

Another genetic possibility, intriguing but unproved, is that certain individuals have a deficient hypothalamic response to acute inflammation. It may postulated that a genetic impairment in hypothalamic-pituitary-adrenal responsiveness to inflammation would be sufficient to permit symmetric synovitis to develop and proliferate and eventually to become a self-sustaining process that we diagnose as RA ***(Schrohenloher, 1991).***

2- Environmental factors in RA :-

If RA were entirely genetic, there would be complete concordance for the disease in monozygotic twins, which is not the case. Even individuals with all the necessary genetic factors to develop RA, such as the identical co-twins of patients with the disease, do so less than half of the time, indicating that non-genetic factors are crucial to the development of the disease ***(Wordsworth and Pile, 1994).***

Bacteria, Viruses, and their Components :-

The idea that infection could provoke the development of RA has been attractive for a long time. However, most of the available evidence for this is conjectural or anecdotal. The identification of *Borrelia burgdorferi* as the causative agent for Lyme arthritis and the finding of microbial antigens in the synovium of reactive arthritis have both accelerated the search for a microbiological cause for adult RA ***(Alspaugh and Tan, 1975).*** Despite this enthusiasm, epidemiological studies do not support a major role for infection in the etiology of RA ***(Silverman and Schhumacher, 1981).***

Two important hypotheses invoking possible microbiological organisms for RA have been proposed. Firstly, tissue damage could result from the chronic inflammatory processes stimulated by persistent infection of the joint by an organism that has so far eluded detection. Secondly, The organisms responsible for triggering the disease may only be present in the early phase of inflammation, and are then rapidly cleared by the immune system. However, once stimulated, the immune system becomes perpetuated as it is redirected against self-antigens present within the joint ***(Silverman and Tan, 1975).***

Epstein-Barr virus (EBV) :-

In ***1975, Alspaugh and Tan*** described an antibody in the sera of patients with RA that reacted with an antigen extracted from a lymphoblastic cell line carrying the EBV. Antibodies named rheumatoid arthritis precipitin were indeed directed against EBV-specific antigens. Although it was demonstrated that there was an abnormally elevated frequency of EBV-infected B cell in blood of patients with RA, it was also shown that in patients with early RA, titers of antibody to EBV-associated nuclear antigen or to viral capsid antigen were not elevated, suggesting that EBV infection was a sequel to and not the cause of RA.

Parvovirus and RA :-

A small particle resembling parvovirus in morphologic, and physical and chemical properties has been derived from rheumatoid synovial tissue. Polycolonal antibodies developed against this putative virus were able to detect reactive antigen and synovial cells from RA patients, but not from individuals with osteoarthritis. Despite these cases, however, it is important to point out that very few rheumatoid patients have evidence of such a coincident infection; in a total of 69 patients with RA, only 4 acquired the parvovirus infection near the time of onset of their RA ***(Cohen et al., 1986).***

Lentiviruses :-

Lentiviruses are a subfamily of retroviruses and derive their name from the slow time course of the infections they cause in humans and animals. The human immunodeficiency virus (HIV) is one of these. Pathologic changes in lentiviruses infections are indirectly mediated by the immune and inflammatory responses of

the host. A deforming arthritis in goats and sheep is caused by lentiviruses, which are difficult to find, although known to be the cause of the disease ***(Haase, 1986).***

Rubella virus :-

Because rubella virus and the rubella vaccine have caused a synovitis in humans, there is interest in this virus as a triggering agent. In one series, 21 instances were reported in which live rubella virus was isolated from 6 patients with inflammatory oligoarthritis. Non of these patients, however, had the classic polyarticular involvement seen so often in RA ***(Grahame et al., 1983).***

Heat shock proteins :-

Reactivity to the mycobacterial 65 KDa heat shock protein (HSP 65) has been implicated in the pathogenesis of adjuvant arthritis in the rat, and may be implicated in the pathogenesis of RA or other autoimmune diseases in humans ***(Karopoulos, 1995).***

The possibility exists of cross-reactive epitopes; HSP from bacteria have "molecular mimicry" with numerous human proteins. More interestingly, yet more complex, is the hypothesis that antibodies and T cell exist that recognize epitopes shared by HSP of both infectious agents and host cells; in inflammation of the joints, synovial cells would express HSP, and these would be recognized by cross-reactive T cells and antibodies ***(daSilva, 1991).*** Thus, it would not matter which microbe in the environment appeared in particular patient, but rather whether the immunogenes would facilitate cross-reactivity of lymphocytes with HSP of host cells ***(Karopoulos, 1995).***