INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune connective tissue disorder, which has variable clinical manifestations that range from mild to life-threatening [1]. These can be characterised by multiple organ damage, very high titres of autoantibodies and immune complex deposition. Interestingly the former of these characteristics may precede the clinical manifestations of SLE by many years [1]. It is well recognised that the probable influence of oestrogen hormonal effect in women during childbearing years increases their chances of developing SLE by 10-15 times [2-5]. The immunopathogenic hallmark of SLE is the polyclonal B cell activation, which leads to hyperglobulinaemia, autoantibody production and immune complexes. All of these factors contribute to the conventional belief that SLE is a disease primarily of these autoantibodies and immune complex deposition, the latter contributing to inflammation by virtue of complement activation and the engagement of complement and fragment crystallisable (Fc) – receptors [6, 7] ultimately inflicting injury to a variety of organ systems (Figure 1). Mediation of these inflammatory responses is characterised by the influx of various cell populations and also to a large extent by the generation of proinflammatory cytokines. The clinical manifestations in inflammatory diseases such as SLE and rheumatoid arthritis (RA) are thought to be influenced by the balance between proinflammatory and anti-inflammatory cytokines [9].

Cytokines are soluble factors and are mainly produced by helper T (Th) cells. They also play a crucial role in the differentiation, maturation and activation of various immune cell types [9]. In order to monitor disease activity and predict disease severity certain cytokines may act as biomarkers [9]. Recent work for example, using microarray techniques and genetic analysis has strengthened the association between cytokine dysregulation and SLE [10]. These breakthroughs show some promise in understanding the immunoregulatory networks of autoimmune diseases, which are influenced by multiple factors, particularly in regard to these cytokines and their interactions.

Through systematic review of published literature, only those cytokines that have significant involvement in the pathogenesis of SLE in the ‘human model’ and those that represent a relatively easy target for therapeutic intervention (i.e. the anti-cytokines) will be reviewed.

PATHOGENESIS AND FUTURE TREATMENTS OF SYSTEMIC LUPUS ERYTHEMATOSUS: THE ROLE OF CYTOKINES AND ANTI-CYTOKINES?

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Cytokine Production and Cytokine Levels in Patients with SLE

Several cytokines are involved in the pathogenesis of SLE [11] and more than 30 years ago [12] immune interferon (IFN-γ) was found in the serum of patients with SLE and showed a good correlation between IFN-γ titres and disease activity. T-helper cells 1 (Th1) cytokines such as IFN-γ, IL-12, and T-helper cells 2 (Th2) cytokines IL-4, IL-6 and IL-10 are each considered to play a role in the course of human SLE [13, 14]. Other proinflammatory cytokines such as IL-1, IL-17, IL-23 and tumour necrosis factor alpha (TNFα) [15] are also involved along with these Th1 and Th2 cytokines.
1. Interleukin 6 (IL-6)

IL-6 is a proinflammatory cytokine which is synthesised principally by monocytes, fibroblasts and endothelial cells (Figure 2). IL-6 secretion can also be found in both T and B lymphocytes [15] and its production is stimulated by IL-1, IL-2 and TNF-α, but subdued by IL-4, IL-10 and IL-13. In combination with type 1 interferons, one of the most important effects of IL-6 is to activate B lymphocytes, drive plasma-cell differentiation and to augment the immunoglobulin secretion [16, 17]. Additionally, IL-6 acts on multipotential progenitor cells, is a neutrophil activator and stimulates megakaryocytes to produce platelets. It also induces terminal macrophage and osteoclast differentiation as well as pyrexia and the production of acute phase proteins [36].

In total contrast to these proinflammatory effects, IL-6 is also involved in a number of unique anti-inflammatory reactions. For example, IL-1 and TNF-α stimulate the synthesis of each other as well as IL-6, however, the latter is involved in terminating this reaction as well as being involved in the upregulatory inflammatory cascade [17].

The association of IL-6 in the pathogenesis of SLE in humans is still controversial [18] although support for this association has been published using several murine models [19-21].

1.1. Role of IL-6 in Human SLE

Human SLE patients have been shown to have increased IL-6 [22-24] levels that are allied to disease activity [23] or anti-DNA levels [22], in some but not all studies [24].

In one study [25], SLE patients had a significantly higher frequency of IL-6 secreting peripheral blood mononuclear cells (PBMCs) compared to those of healthy controls. This may well be due to environmental factors as exposure to UV light has been shown to stimulate the monocyte/macrophage fraction of PBMCs taken from SLE patients to produce IL-6 [26]. Another interesting observation was that lymphoblastoid cells that were isolated from SLE patients exhibited high levels of IL-6 and blocking IL-6, which resulted in the inhibition of anti-dsDNA production in vitro [27]. However, using a widely applied method to study the activation of the innate immune system i.e. the in vitro stimulation of whole blood using lipopolysaccharide (LPS), IL-6 production was significantly lower in SLE patients as compared to normal individuals [28].

Unlike normal individuals, B lymphocytes from SLE patients were found to spontaneously generate large amounts of immunoglobulins (Ig). There was however, a significant reduction in this Ig production when IL-6 was blocked and this production was only restored after exogenous IL-6 administration [29]. In addition these B lymphocytes also secrete anti-double-stranded DNA (anti-ds DNA), with different B lymphocyte populations contributing to this in a number of different ways. For example, it was shown that the majority of these autoantibodies were produced ex vivo by low density B lymphocytes [29], whereas high density B cells had little effect. It was also shown that in response to IL-6, low density B lymphocytes from patients with active SLE were capable of directly differentiating into Ig secreting cells [30].

CD5 expression is also down-regulated by IL-6 via DNA methylation, which promotes activation and subsequent expansion of auto-reactive B cells seen in SLE patients [30]. The IL-6 abnormalities seen in SLE may well be due, in part to, genetic differences. For example, Linker-Israeli et al [31] demonstrated that alleles of the adenine/tyrosine (AT) rich minisatellite situated in the 3’ region flanking the IL-6 gene, was associated with SLE patients of either Caucasian or African-American origin, but not in the control group.
It is well proven that the classical marker auto-antibodies seen in SLE are anti-ds DNA antibodies and although the titre of those antibodies in the serum of SLE patients can be a reflection of disease activity in lupus nephritis, for example, their exact role remains unclear. It has been shown however, that anti-dsDNA can have a direct effect on cytokine expression in a variety of cells. They can also upregulate the expression of the proinflammatory cytokines IL-1 and IL-6 in endothelial cells \[32-34\] and they can stimulate the expression and release of IL-1, IL-6, IL-8, IL-10 and TNF \[35\] (from human resting mononuclear cells).

1.2. IL-6 and lupus nephritis

IL-6 has been shown in several studies to have proliferative effects on mesangial cells thereby modulating injury in immunologically generated nephritis. Two studies demonstrated that mesangial proliferation in mesangial proliferative glomerulonephritis correlated well with the urinary IL-6 levels \[37, 38\]. Further studies demonstrated high urinary excretion of IL-6 in patients with active lupus nephritis. The levels of IL-6 were significantly elevated in patients with proliferative lupus nephritis (World Health Organisation (WHO) Class III and IV) with concomitant high titres of anti-dsDNA antibodies \[39, 40\]. IL-6 levels were also found to be much higher in patients with active nephritis as compared to those patients with dormant renal disease \[24, 40\]. Additionally it was found that there was an enhanced *in situ* expression of IL-6 in lupus nephritis, mainly along the renal glomeruli and tubules \[41-43\].

Interestingly IL-6 has also been shown to have a positive association with the Neuropsychiatric syndromes of systemic lupus erythematosus (NPSLE). For example elevated levels of IL-6 have been reported in the cerebrospinal fluid (CSF) of patients with NPSLE, without subsequent damage to the blood-brain barrier \[44-46\].

To summarise, IL-6 has an important role in mediating local inflammation and insults of various tissues.

1.3. Therapeutic Implications of IL-6 in SLE

As previously stated in a number of studies, IL-6 was found to be elevated in both human and murine lupus \[21-24\]. IL-6 released from PBMC for example, directly correlated with disease activity and the treatment response seen in lupus nephritis patients \[47\].

Other studies have confirmed that there was an increased expression of the IL-6 agonistic receptor gp130 on peripheral lymphocytes in SLE patients, and that the levels correlated with overall disease activity \[47, 48\].

Taking this into account it has been suggested that gp130 could be a useful biomarker to monitor both the activity of disease and subsequent treatment responses in those patients \[49\].

Using murine models where the success of IL-6 antagonism is well proven, a phase 1 dose finding study was set up to evaluate the use of a monoclonal antibody tocilizumab (Anti-IL-6 R Ab) in human SLE patients \[49\]. A total of sixteen patients with moderately active disease (as defined by the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), i.e. a SELENA-SLEDAI score of between 3 and 10 or active glomerulonephritis) were given tocilizumab in one of three doses (2 mg/kg in 4 patients, 4 mg/kg in 6 patients, and 8 mg/kg in 6 patients) twice weekly for 12 weeks. Patients were then monitored for an additional 8 weeks \[50\].

There was a notable reduction in inflammatory markers, auto-antibody levels and in disease activity (SELENA-SLEDAI from 9.5 at baseline to 5.5 at 20 weeks) with a median decrease of 38% in the 4 mg/kg dosage group and 56% in the 8 mg/kg dosage group. Unfortunately almost all the patients developed a significant dose-related neutropenia with concomitant high rates of infections \[50\].

Although neutropenia may limit the maximum dosage of tocilizumab in patients with SLE, the observed clinical and serological responses are promising and warrant further studies to establish the optimal dosing regimen and efficacy.

2. Interleukin 10 (IL-10)

The cytokine IL-10 is mainly produced by lymphocytes and monocytes. It also impedes the activation of antigen presenting cells (APCs) and down-regulates the expression of co-stimulatory molecules such as major histocompatibility complex class II (MHC II) and B7 expression \[51\]. IL-10 also inhibits T cell function by diminishing the expression of other proinflammatory cytokines such as TNFα, IL-1, IL-6, IL-8 and IL-12 \[52, 53\]. In addition to these inhibitory functions IL-10 boosts B cell mediated proliferation, thereby increasing survival, proliferation, differentiation and immunoglobulin class switching, resulting in increased antibody secretion, which promotes the inflammation seen in SLE \[54\].

In particular, the production of IL-10 and TNFα, two mutually associated cytokines, play a complex and opposite role in these systemic inflammatory responses that has been found to be deregulated in SLE patients (Figure 3).

All these findings, plus the addition of environmental influences are suggestive of a combination between genetic and disease-induced events. IL-10 and TNFα for example, have been linked to SLE and genetic polymorphisms at the promoter regions of both these genes \[55\] is associated with their over production, particularly that of IL-10 \[56\]. However, previous studies of a much larger magnitude which included patient family members with increased IL-10 production \[57\], failed to confirm this association \[58\].

Increased IL-10 production might also explain B cell hyperactivity and autoantibody production, two of the main indicators of the immune dysregulation seen in SLE.

In line with this; the association between IL-10, disease activity, immune complexes isolated from the serum of SLE patients as well as monoclonal anti-dsDNA antibodies, induced IL-10 production in healthy monocytes \[58, 59\]. IL-10 might also regulate dendritic cells (DCs) and T cell function, by promoting Th2 deviation of the overall immune response (Figure 3) \[60\].

2.1. Therapeutic Implications of IL-10 in SLE

Although one of the major factors is still the absence of a therapeutic agent which is suitable for long-term administration in human patients with SLE IL-10 was the first cytokine to be blocked \[61\], which has led to use of anti-IL-10 antibody in the treatment of this disease \[61\].

An over-production of IL-10 has been demonstrated in murine models of SLE \[62\]. Using continuous early-onset therapy with an anti-IL-10 antibody however, delayed autoimmunity in NZB/W mice and improved their overall survival rate from 10 to 80% \[63\]. In a pilot study using an anti-IL-10 murine monoclonal antibody (MoAb), which neutralizes human IL-10, Llorente et al. \[64\] evaluated the clinical efficacy and safety of this antibody in a total of six patients with steroid dependent SLE.
The treatment consisted of administering 20mg/day of MoAb intravenously for a total of 21 consecutive days. The patients were then followed up monthly for a total period of 6 months. The therapy was well tolerated in all six patients and although all had significant improvement of their cutaneous lesions and/or joint symptoms during MoAb administration, they also developed antibodies against it. This study not only suggests that the use of MoAb may be of benefit in the management of refractory SLE, but that a much larger, randomized and blinded study using a humanized anti-IL-10 MoAb is required. Such an agent might soon be available.

3. Interleukin 17 (IL-17)

IL-17 is an ancient cytokine, and is a type I transmembrane protein, produced by activated T cells and is intimately related to epithelia, especially those of the intestinal mucosa. IL-17 is a potent pro-inflammatory cytokine that also plays an important role in the immune response against fungi and bacteria. As stated, IL-17 is produced by activated T lymphocytes, with the ‘Th17’ cells being the most energetic producer. Th17 cells originate when naive CD4 T cells are primed in the presence of transforming growth factor (TGF-β) and other important inflammatory cytokines including IL-6, IL-21 and IL-23. The latter also enhances IL-17 production by memory T cells. These observations strongly suggest that the presence of an inflammatory signal of some sort is required to transform these naïve CD4 T cells to become pro-inflammatory. The cytokine IL-21 for example, was found to influence Th17 differentiation. Unlike IL-6 it is produced by Th17 cells and the T-follicular helper cells, but not by APCs. Mangan et al. claimed that one of its functions was that of an auto-amplifier of the Th17 response. IL-17 also upregulates the expression of intercellular adhesion molecule-1 (ICAM-1) through the facilitation of T cell activation and infiltration into tissues. Th17 cells can also assist as an independent T helper effector cell subset, which promote an inflammatory response through cytokine secretion (i.e. IL-17A, IL-17F, IL-21 and IL-22) (Figure 4). In regard to the pathogenesis of SLE, this collection of cytokines can stimulate B lymphocytes, to initiate the local inflammation and tissue injury often seen in this disease. Recent studies support and confirm the role of IL-17 in SLE pathogenesis.
3.1. Role of IL-17 in Human SLE

Current evidence suggests that SLE patients have abnormally high levels of IL-17 and IL-23 in their serum [75, 76] and that the level of IL-17 correlates with disease activity [75, 77]. In a recent study Crispin et al [78] demonstrated that a significant portion of IL-17 in SLE patients was derived from double negative (DN) TCR-αβ+CD4-CD8- T cells. DN T cells represent a small subset in healthy individuals, whereas in the peripheral blood of SLE patients these cells represent a much larger component producing proinflammatory cytokines including: IL-17, IFN-γ and IL-1β [78] (see Figure 1). These DN T cells and Th17 cells have also been seen in renal biopsies of patients with lupus nephritis, adding credence to their pathogenic role in renal lupus [74].

As well as its direct proinflammatory activities, IL-17's effects in other cell types may also contribute to SLE pathogenesis. Dong et al [79], for example, observed that there was an increased production of total IgG, anti-dsDNA IgG and IL-6 by peripheral blood mononuclear cells of patients with lupus nephritis, adding credence to their pathogenic role in renal lupus [74].

4. Interleukin 23 (IL-23)

IL-23 plays an important role in the development of pathogenic Th17 cells and the subsequent production of IL-17 [86-88] (Figure 4).

IL-23 is a type 1 covalently linked heterodimeric cytokine comprising of p19 and p40 subunits, which are shared with IL-12 (Figure 5). IL-23 is produced in the main by both activated dendritic and phagocytic cells [89, 90] and recent studies suggest that rather than IL-12 it is the most important cytokine for the pathogenesis of autoimmune diseases [91, 92]. IL-23 and IL-12 share a common p40 subunit, which binds to a common IL-12 receptor β1. Activated/memory T cells, T-cell clones and natural killer cell lines in humans, preferentially express the IL-23 receptor (IL-23R), which is made up of the IL-23 complex, and a common IL-12 receptor β1. Because of its central role in the pathogenesis of various autoimmune diseases including inflammatory bowel disease, Duerr et al [93] and ankylosing spondylitis [96, 97], studies focusing on its role in SLE have arisen.

Statins which are used extensively in lowering cholesterol in humans have been shown to have immune-modulatory effects and have recently emerged as possible therapeutic agents for autoimmune disease including SLE, although results in animal models have been both conflicting and controversial [82, 83]. It was demonstrated that statins could suppress the secretion of IL-17 by Th17 cells [84] and that they have beneficial effects in improving the rate of progression of chronic kidney disease in human SLE patients with lupus glomerulonephritis [85].

Figure 4: Proposed model for the role of T-helper type 17 (Th17) cells and interleukin (IL)-17 in the pathogenesis of systemic lupus erythematosus (SLE) (reproduced with permission [72]). CD4+ cells differentiate into Th1, Th2 and Th17 effector cells as well as double-negative (DN) T cell subsets. The cytokine milieu characteristic of SLE patients (lack IL-2; high levels of IL-6 and IL-21) could promote Th17 expansion. Th17 cells serve as an independent T helper effector cell subset promoting inflammation through cytokine secretion. The signature cytokines include IL-17A, IL-17F, IL-21 and IL-22. These cytokines have stimulatory effects on B cells and activate local inflammation and tissue damage leading subsequently to the pathogenesis of SLE [72].
4.1. Role of IL-23 in Human SLE

As stated earlier, cytokine-mediated immunity plays an important role in the pathogenesis of SLE, and implications of this are seen in animal models. Additionally, a number of studies in human SLE have also shown a need to focus on IL-23 and its receptor. Wong et al. [75], confirmed that ex vivo syntheses of IL-17 by IL-23 or IL-18 produced from co-stimulated lymphocytes was much higher in patients with SLE than the control group and increased levels of IL-12, IL-17 and Interferon-inducible protein-10 (CXCL 10) had both significant and positive correlations with SLEDAI [75]. It was also shown by Huang et al. [96] that in active SLE patients, the mRNA levels of p19, p40 of PBMC were significantly higher when compared with levels in their inactive counterparts [96]. In another study, Hillyer et al. [97], reported that in Rheumatoid Arthritis (RA) synovial cultures, IL-23R blockade resulted in a significant inhibition of TNF-α (57%), IL-1β (51%) and IL-6 (30%) [97]. All of these results suggest that IL-23 may have pathogenic activity in a proportion of the patients tested that have late-stage RA. In a recent study, Kwan et al. [98] examined the urinary sediment of three groups of subjects: those with active SLE, with history of lupus nephritis in remission, those with no history of renal involvement SLE and healthy individuals. In each case they quantified the mRNA expression of IL-17, IL-23 and other Th 17-related cytokines. The results concluded that the urinary expression of Th-17 related genes was increased in the SLE patients when compared to the control group. The degree of this up-regulation however, was inversely proportional to the disease activity [98]. This pattern was contradictory to previous studies on the urinary mRNA expression of Th1- and Th2-related genes [99, 100], which showed an up-regulation of Th1-related genes and a down-regulation of Th2-related genes in patients with SLE, with the magnitude being proportional to overall disease activity. Although these findings suggest a regulatory role of IL-23 in the pathogenesis of SLE, further studies are required using a larger sample size in different populations, to confirm this association [101].

4.2. Therapeutic Implications of IL-23 in SLE

At present the majority of the data in regard to IL-23 have come from studies using murine models, which may not be wholly relevant for human SLE. There is however growing evidence that in the human model IL-23 plays a role in the development of the disease and that the use of anti-IL-23 therapy to treat the subset of SLE patients that are characterised by high levels of IL-23 is now a distinct possibility [81]. There are two issues that need to be taken cognisance of in this regard. Firstly, both IL-23 and IL-23R are critical in mediating antimicrobial defences and in cross-regulating other cell subsets, therefore the risk of infectious complications need to be taken into account. Secondly most of the data regarding IL-23 have been from murine models. Further comprehensive studies are therefore required, especially in regard to the therapeutic potential of IL-23 in the treatment of human SLE.

5. B-lymphocyte Stimulators (BlyS)

The B-lymphocyte stimulator (BlyS also known as the B cell activating factor belonging to the TNF family, or BAFF) [102] was identified as a novel TNF family ligand almost 10 years ago [102-105] where it was found to be the key in both the selection and survival of B cells. The expression of the BlyS protein is confined to myeloid lineage cells (e.g. monocytes, macrophages, dendritic cells and activated neutrophils) [106-108]. Although the levels of BlyS are well established and constant, its expression and secretion can be increased by inflammatory cytokines, such as IL-2, TNF-α and IFN-γ [107, 109, 110]. BlyS can bind to three types of receptors: BlyS receptor 3 (also know as BAFR), transmembrane activator-1 and calcium modulator and cyclophilin ligand-interactor (TACI) and B cell maturation antigen (BCMA). It has been shown that BlyS can bind to all

![Figure 5: A schematic diagram of the different components making up the IL-12 and IL-23 receptors and the common STAT4 activation pathway.](image-url)
these three receptors on B cells, as opposed to a proliferation-inducing ligand (APRIL), which can only engage to TACI and BCMA [111]. The most important receptor amongst the three was found to be BAFFR as it is was the one that mediated most of the Blys effects.

5.1. Implications for B cells and Blys in Human SLE

Elevated serum levels of Blys protein have been observed in patients with autoimmune disease, including those with SLE and these levels correlated with their anti-dsDNA levels [112-115]. In one study where the serum Blys levels and disease activities were measured; healthy controls had normal serum Blys levels over time, compared to SLE patients who had escalating levels. Results displayed a persistent elevation in 25% of patients tested and an intermittent elevation in another 25% of patients [116]. These findings suggest that Blys may figure significantly in the development of autoimmune disease and in particular SLE, thus making it an ideal target for SLE therapy.

5.2. Therapeutic Implications of Blys in SLE

There are many conflicting reports regarding Blys-targeted therapy using belimubam, a fully human monoclonal antibody (lgG1) that binds to Blys and inhibits its biological activity. In a phase I randomised controlled clinical trial [117], the safety and efficacy of belimubam in SLE patients was studied. Although there was a reduction in CD20+ B cells in this dose-ranging study as compared to the placebo, there was no significant improvement in disease activity as assessed by the SLENA-SLEDAI score. In a phase II dose-ranging study [118], three different doses of belimubam were evaluated in SLE patients who were randomised over a 52 week period and again there was no significant difference between the combined belimubam group versus the placebo group. A total of 71.5% of the patients were aninuclear antibody (ANA) positive and interestingly in the subgroup that were ANA positive the SLEDAI score was reduced by 29% at week 52. This trial was later continued as an open-label extension study and a four-year safety and efficacy for these patients has also recently been published [119] where serologically active patients had sustained improvement in their flares over time. There was also a decline in multiple pathogenic antibodies, including anti-dsDNA and anticardiolipin. Multi-centre phase 3 trials, of BenlystaTM (belimubam) (BLISS-52 and BLISS-76) in seropositive patients with SLE are currently being evaluated in two large randomised, double-blind, placebo-controlled studies [120]. The results of these two pivotal phase 3 trials, suggest that belimubam can reduce SLE disease activity and that it may be the long-awaited new effective therapy for this disease.

6. Type I Interferons (Type I IFN)

Although type I and type II IFNs have both been implicated in the pathogenesis of human SLE [121-125], the type I IFNs are regarded as the most important. For example the initial symptoms in many patients with active SLE are often flu-like, where they exhibit symptoms such as fever and fatigue, both of which reflect high serum type I IFN levels, which is also relevant to overall disease activity and severity [126-128]. The classical triggers of type I interferon are viral DNA and RNA with signals being mediated via the Toll-like receptors (TLR) or the retinoic acid inducible gene I (RIG-I) like receptors [129]. Although type I IFNs are manufactured by all leucocytes, the major producer is the cell subset; plasmacytoid dendritic cells (PDC) in response to TLR7 or TLR9 activation [130].

In a previous study the results showed no over-expression of the type I IFN gene in the blood from SLE patients whereas an over expression of several other IFN-inducible (IFI) genes has since been found [131]. This finding was in agreement with other studies, which demonstrated that peripheral blood from SLE patients had remarkable homogeneous gene expression patterns, including an over expression of IFI genes, implying IFN involvement in SLE [132-134].

Hopefully in the future, genetic mapping may be of assistance in predicting the development and severity of the disease and that IFN regulated cytokines may also be used to monitor disease activity and subsequent organ damage [137-138]. The effect of a single dose of anti-IFN monoclonal antibody in SLE patients was evaluated in a phase I dose-escalation study [139]. The results noted a reduction in disease activity where the over expression of IFN-inducible genes were neutralised in a dose-dependent manner. In addition, a number of doses had clinical benefit in terms of SLEDAI. Currently there are two phase 2 trials taking place to evaluate the effects of anti-IFN monoclonal antibody in SLE patients [140, 141].

7. Tumour Necrosis Factor-α (TNF-α)

Tumour necrosis factor- alpha (TNF-α) is a proinflammatory as well as an immunoregulatory cytokine. It is expressed as a homotrimer on the cell surface in a soluble form after the activation of macrophages and dendritic cells, (Figure 3) with divergent effects on the immune system in SLE [142, 143].

7.1 Role of TNF-α in Human SLE

The significance of TNF-α in the pathogenesis of SLE remains controversial as one might argue that it is beneficial and that TNF blockade would be unfavourable. However, the in vivo data ascertained from a number of SLE patients suggests the contrary.

The levels of TNF-α are actually increased in the serum of SLE patients and are closely correlated with overall disease activity, where an abundant TNF-α expression was demonstrated in lupus nephritic kidneys [146, 47]. The beneficial effects of TNF-α blocking therapy have been shown in a series of studies in patients with other autoimmune diseases, but the results were conflicting in that these patients developed antinuclear factors, anti-ds DNA and anticardiolipin antibodies as well as a lupus-like syndrome [147, 148]. All symptoms and autoantibodies disappeared when TNF-α blocking therapy was discontinued.

Nevertheless, the findings of elevated serum TNF-α in active SLE and the over expression of TNF-α in active lupus nephritis [47, 149] provided the rationale for using TNF-α antagonism in SLE patients [145, 150, 151].

Unfortunately, long term treatment using TNF-α blocking therapy was associated with high rates of serious adverse reactions [152-155]. For example in two randomised trials [156, 157] that were designed to evaluate the efficacy and safety of the TNF inhibitors; infliximab and etanercept in SLE patients, both had to be terminated prematurely.

Taking all of this recent information into consideration it is highly unlikely that TNF inhibition will be used routinely in the treatment of SLE.

8. Concluding Remarks

This review has discussed a vast amount of information in regard to the pathogenic link between the various cytokines
and SLE (Figure 6) as well as new approaches that target the pro-inflammatory cytokine pathways which lead to the amelioration of clinical disease in human SLE. However, the elicited inflammatory response characterised by both the influx of various cell populations mediated to a large extent by the generation of these proinflammatory cytokines still needs to be fully elucidated. Most of the recent trials have dealt with the use of agents that target the cytokines involved in this inflammatory chain of events in the induction phase of severe disease, or in symptoms refractory to conventional treatment such as corticosteroids. They may therefore offer an advantage in achieving rapid disease control and minimise corticosteroid use. The role of these agents in the maintenance phase of SLE still remains undefined, and whether the interference of these events becomes an important therapeutic target will depend on the results of ongoing and continuing clinical trials. Given the safety concerns regarding the long-term use of such agents especially in SLE, where complications of infection and malignancy may arise, the major challenge for the future will be to define which one of these targets will actually be useful in the management of this disease.

![Figure 6: Simplified schematic diagram showing the complex interactions between various immune cells and cytokines which lead to the pathogenesis of SLE. (reproduced with permission)](image_url)

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**Peer reviewed ORIGINAL ARTICLE**

### INTERACTION BETWEEN NK CELLS AND HLA-G1 AT THE PLACENTAL INTERFACE OF HIV-1 INFECTED PREGNANT WOMEN: ADDITIONAL RISK FACTORS OR PHYSIOLOGICAL ASSOCIATION?

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**ABSTRACT**

**Background:** Human Leucocyte Antigen-G (HLA-G) molecules are involved in the inhibition of cell-mediated immune responses and could promote the propagation of HIV-1 infection across the placental interface thus increasing the risk of vertical transmission. Therefore, the objective of this study was to assess whether the Major Histocompatibility Complex (MHC) - coded molecule HLA-G inhibits Natural Killer (NK) cell activity thereby, assisting viral penetration across the placental barrier in HIV-1 positive pregnant women.

**Study Design & Methods:** Natural Killer (CD56⁺) cell activity and placental HLA-G1 expression was assessed using immunohistochemistry and real-time polymerase chain reaction (RT-PCR) techniques, respectively. Studies were performed on a total of fifty five placental samples obtained from HIV-1 infected mothers at birth.

**Results:** Low numbers of NK cells increased risk of vertical transmission [OR = 3.424 (95%CI 0.65-17.89)]. The risk of babies becoming infected increased by 1.3 with every 1 unit increase in HLA-G1 expression. A positive correlation was observed between mothers’ log viral load and transmission of infection to the baby (p = 0.047; 95%CI 1.029-11.499).

**Conclusion:** Low NK cell activity at the placental interface increased the risk of vertical transmission. Maternal viral load remained a strong predictor of viral transmission.

**KEYWORDS**

Natural Killer cells (CD56⁺), Human Leucocyte Antigen-G1, vertical transmission, viral load, up regulation.

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**INTRODUCTION**

Natural Killer (NK) cells are a population of low-density, large granular lymphocytes, which mainly develop and differentiate in bone marrow and then enter into the circulation. These cells comprise approximately 5-20% of peripheral blood lymphocytes and are involved in the innate immune response against certain microbial, viral and parasitic infections [1, 2]. In response to proinflammatory stimuli, which may be induced by a viral infection, NK cells migrate to various tissues and organs of the body. In the mucosal decidual tissues of the maternal uterus, NK cells are the most abundant class of lymphocyte,