Systemic lupus erythematosus

LSC301 Clinical Biochemistry and Cellular Pathology, Unit 2

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Research a specific chronic inflammatory condition and identify the main drugs used to treat the condition. Draw up a table of different drugs with their biochemical target/s Select 2 treatments that are effective via different targets. Describe and compare their modes of action (you might want to do this with the aid of a diagram) in terms of the impact on inflammation. Critically discuss the wider impact on patient health of your two selected treatments.

Systemic lupus erythematosus (SLE) is a chronic condition that induces skin rashes, joint pain, and tiredness. It is an autoimmune disease, and consequently, the immune system attacks wrongly healthy body areas. The origin of lupus is not completely understood; however, it can be caused by viral infection, genetic predisposition, childbirth, puberty, menopause, sunlight, and some medicines. In fact, it is more popular between women, Asian and black, than men (NHS, 2020).

There is no existing cure, but symptoms may be improved if prompt treatment is undertaken. It is challenging to diagnose due to its similarity between the symptoms of other conditions and the symptoms shown in this condition. Significant level of antinuclear antibodies in a blood test and the display of common symptoms, means it is likely lupus. These depend on the level of severity of the disease, which can go from mild to severe. Mild lupus targets skin and joint problems and tiredness; moderate severity includes inflammation of several body parts such as skin, joints, liver, heart, lungs, and kidneys; and finally, severe lupus is express through significant inflammation which causes damage to the heart, brain, lungs and can be fatal. The symptoms of these conditions can flare up after treatment and can become worse for some time before they remit. The cause of this fluctuation is unknown. However, some patients experience constant symptoms (NHS, 2020).

The loss of immune tolerance to self-antigen occurs in the clinical onset of SLE. This is due to the interaction of proinflammatory stimuli such as different cytokines and type 1 interferons, other hormonal and immunological factors, environmental precipitants, and genetic predisposition (Fava & Petri, 2019). Numerous genes are associated with a tendency of developing lupus, usually encoding for immunological components such as IRF5, STAT4, CTLA4, BLK, HLA. SLE shows a significant heritability, a genetic susceptibility is indicated by the 11-50% concordance between monozygotic twins and the higher prevalence in families. This suggests that genetics play a significant role in the development of this condition (Generali et al., 2017). Autoimmunity acts by inducing a complicated interplay of apoptotic waste clearance and immune processes besides neutrophil action and interferon pathways among others (Tsokos et al., 2016).

It is known that disruption of both the adaptive and innate immune system is induced by lupus. T cells are compromised, failing to make enough IL-2, and producing an excess of double-negative T lymphocytes. This provides immoderate help to B cells (Katsuyama et al., 2018). Consequently, an excess of B cells reaction induces B cell lymphopenia, which is the outcome of cytokine-mediated apoptosis of CD4 and CD8 T cells, B cells, and dendritic cells observed in sepsis. The innate immune system plays a key role in recognizing a strong type 1 interferon to identify lupus (Fava & Petri, 2019).

The main targets of the treatments used to deal with lupus are the prevention of organ damage; reduction of the development of several conditions that lupus induces such as accelerated atherosclerosis; the diminution of pain and fatigue; and activity regulation to maintain the lowest degree possible involving immunosuppression by immunomodulators. These can be corticosteroids, biologic, small molecules and cytotoxic-immunosuppressants among others. The drugs that target SLE act as regulators of the immune system without raising the risk of malignancy or infection (Fava & Petri, 2019). Immunomodulators currently in use include hydroxychloroquine, vitamin D, prasterone (dehydroepiandrosterone synthetized), and belimumab. These kinds of therapies are crucial to modify the immune responses linked with lupus without obvious immunosuppression by acting via many cytokines and cellular pathways (Durcan & Petri, 2016).

Main drugs in SLE

Hydroxychloroquine	Inhibition of B and T cell signalling, antigen presentation and NOX signalling. A reduction in the production of pro-inflammatory cytokines occurs by the inhibition of TLR signalling. It also promotes lysosomal activity increasing pH levels and interferes with MHC-antigen binding (Fava & Petri, 2019).
Vitamin D	Immunomodulatory effects due to vitamin D receptor found in several immune cells such as dendritic cells, activated T cells, and monocytes as well as in vasculature, skin, and other tissues (Fava & Petri, 2019). It also has anti-proliferative effect due to the promotion of Th1 (IL-2, TNF- α, IFN- γ) to Th2 polarization as well as Th17 to Treg state.

	Moreover, it affects the function and development of NKT cells (Fava & Petri, 2019). Furthermore, Vitamin D is an anti-fibrotic molecule. It prevents pro-fibrotic pathways arbitrated by Ras and TGF- β (Fava & Petri, 2019).
Dehydroeipandrosterone	Androgenic steroid that acts on several immunologic pathways and cytokines, therefore it regulates immune function due to its anti-inflammatory effects. Some of these regulator effects have an impact on the modulation of the production of pro-inflammatory cytokine like IL-1, IL-2, TNFa, and IL-6. It has been shown the decrease in IL-10 levels, directly linked with SLE, as it is a B cell stimulatory cytokine (Chang, 2004).
Belimumab	Monoclonal antibody that inhibits the soluble B cells stimulator cytokine. It binds to soluble B cells and prevents the binding with the receptor. For this reason, the binding of soluble B cells to belimumab leads to a decrease in the antiapoptotic proteins production and autoantibody and immunoglobin formation (Dennis, 2011).
Prednisone	Corticosteroid, specifically, a glucocorticoid which reduces inflammation by suppressing the migration of leukocytes and rising capillary permeability. It can also activate several nuclear receptors, and consequently, a prevention of proinflammatory cytokine production (Bergmann et al., 2012).
Cyclophosphamide	An extremely poisonous alkylating agent that diminishes B and T cells and overturns the production of antibodies (Fava & Petri, 2019).
Triamcinolone	Corticosteroid, specifically, a glucocorticoid which shows immunosuppressant and anti-inflammatory activity by preventing the phospholipase A2 enzyme on the phospholipid layer of the cell membrane. This results in membrane failure of leukocyte lysosomes and consequently it inhibits the

	biosynthesis of leukotrienes and prostaglandins (Hannah et al., 2016). Moreover, triamcinolone prevents leukocyte and macrophage migration to the target area by reversing permeability and vascular dilation. It also shows its anti-inflammatory effects via the inhibition of NF-kappa-B and the reduction of IL-8 and IL-6 (Hannah et al., 2016).
Azathioprine	DNA and RNA synthesis inhibitor. In addition, it has a tolerogenic effect due to the inhibition of CD28 mediated signal 2 found in T cells (Fava & Petri, 2019).
Methotrexate	DNA synthesis replication and repair via binding irreversibly to dihydrofolate reductase, reducing the synthesis of purine consequently. Moreover, low doses of methotrexate increase anti-inflammatory adenosine signaling; lower the adhesion of molecules on synovial and endothelial cells; decrease the circulation of pro-inflammatory T-cells; and induce activated lymphocytes apoptosis (Fava & Petri, 2019).
Mycophenolate	This drug gets rid of guanoside nucleotides in B and T cells and inhibits proliferation. It stops monocyte and lymphocyte recruiting to inflamed tissue (Fava & Petri, 2019).
Tacrolimus	T-cell calcineurin inhibitor by forming a complex with protein 12 binding immunophilin FK506. This then prevents the phosphatase activity of calcineurin, and as a result resulting IL-2 transcription is reduced and T cells activated. It also provokes a reduction in the production of IL-4, IL-2, IL-5, TNF-α, and IFN-γ (Hannah et al., 2016).
Rituximab	An anti-CD20 monoclonal antibody that promotes peripheral B cell reduction (Fava & Petri, 2019).
Anifrolumab	Monoclonal antibody that blocks type 1 IFN-α/β/ω receptor, which is the mediator of type 1 interferon signalling. Moreover, this drug

	was linked with improved C3 and reduced anti-dsDNA titers levels (Fava & Petri, 2019).
Ustekinumab	Monoclonal antibody that blocks IL-23 and IL-12. These are shown to be higher in SLE and as a consequence, the overstimulation of B cells is induced. Comparably to anifrolumab, ustekinumab enhanced C3 and lowered anti-dsDNA levels (Fava & Petri, 2019).
Baricitinib	Baricitinib is an inhibitor of JAK2 and JAK 1. The Janus kinases are part of the tyrosine kinases family and these mediate intracellular marking of different cytokines involving the JAK-STAT pathway. JAK1 and JAK 2 arbitrate signalling for type 1 interferons, IL-12, IL-6, IFN-γ and IL-23 amongst others (Fava & Petri, 2019).
Atacicept	Protein that prevents the action of B cells via the inhibition of both BLyS and APRIL (Fava & Petri, 2019).

Treatment

It is certain that SLE is an autoimmunity disease induced by an immune system disfunction. This can cause immune cell overstimulation, the discharge of proinflammatory cytokines and finally the manifestation of disease. B cells play the main role in clinical manifestations of SLE because they are the mediators of tissue inflammation in lupus. For this reason, most clinical trials and pharmaceutical research have been focused on preventing B cell activity (Dennis, 2011).

A recently marketed drug called belimumab was approved as a treatment of patients with SLE. Belimumab is a biologic molecule that was specifically designed for lupus. It is a monoclonal antibody that binds to soluble B-lymphocyte stimulator (Blys) cytokine, so B cells are not activated but they are led to apoptosis (Figure 1) (Dennis, 2011).

On the other hand, hydroxychloroquine is an antimalarial drug discovered in 1630 but used to treat several rheumatic diseases like SLE since 1940. It negatively mediates different aspects of the adaptive and innate responses such as the prevention of B cell activation with the goal of the reduction of inflammation to help minimize autoimmune diseases (Schrezenmeier & Dörner, 2020).

Mechanism of action

As an overview, the first step of the immunopathogenesis of SLE is the autoantibodies released by autoreactive B cells forming complexes with autoantigens that are circulating around. The complements then bind to these complexes and go to the specific tissues to induce inflammation (Dennis, 2011).

Belimumab is involved in the interaction of BLyS and B cells. B-lymphocyte stimulator protein (BLyS) is part of the TNF family of cytokines, and it is a crucial factor to the survival of B cells. BLyS is expressed and quickly divided by myeloid cells and other immune cells. It is attached to receptors on the cell surfaces of autoreactive and normal B-lymphocytes, sending them signals to them to keep them living, maturing, and differentiating into autoantibody and antibody-producing cells. The main role of belimumab is to bind to soluble BLyS to stop it from maintain the communication through receptors on autoreactive and normal B lymphocytes. A decrease in the signaling by BLyS induces an increase in the level of cells that go through apoptosis. This affects inflammation as less B cells will survive, so less cells will be able to produce antibodies that binds to antigens so complement bind into those complexes to induce inflammation (Dennis, 2011).

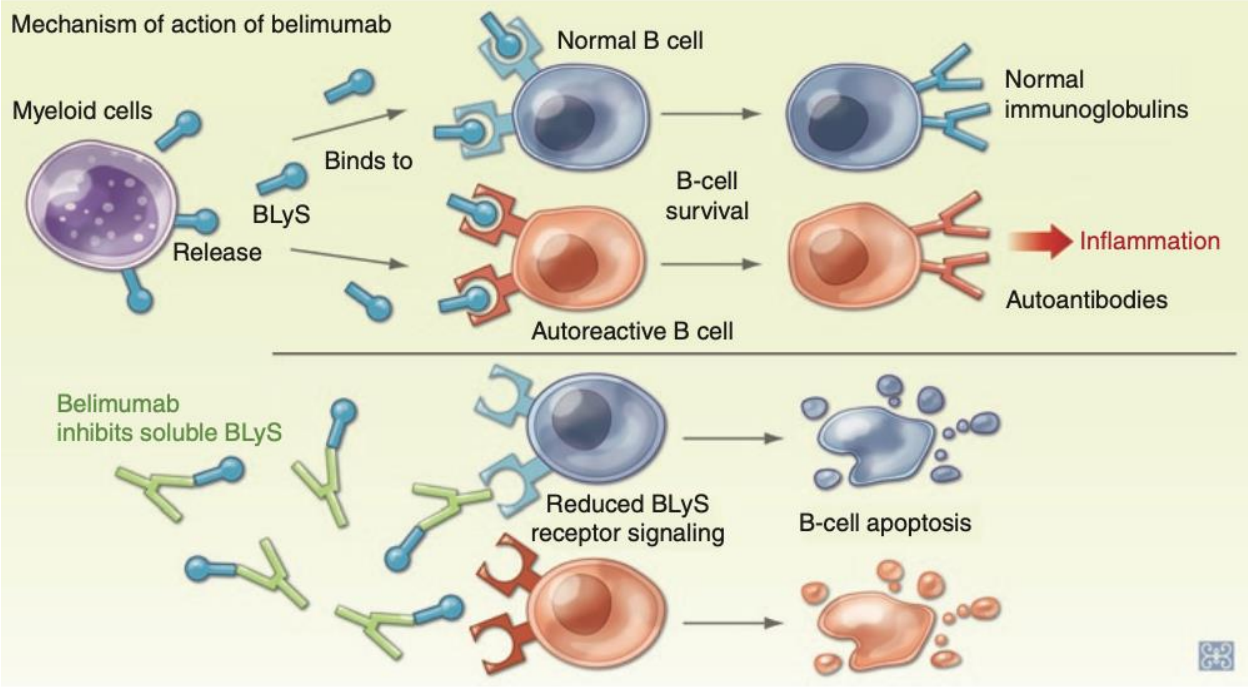

Figure 1: A picture explaining the mechanism of action of belimumab (Dennis, 2011, p.144, figure 1).

On the other hand, hydroxychloroquine influence lysosomal activity, signaling pathways and autophagy. It inhibits TLR signaling by increasing endosomal pH and consequently, it reduces the release of proinflammatory cytokines made by mononuclear cells in the blood such as TNF α, IL-6, and IL-2. Pro-inflammatory cytokines play a role in RA pathogenesis by maintaining chronic inflammatory synovitis, stimulating autoimmunity, and damaging joint tissues. Cytokines like TNF α influence the promotion of B- cell survival and antibody formation, and therefore the process of inflammation is affected. Hydroxychloroquine can prevent T and B cell activation because it also impairs the ability to release of Ca^{+} from the endoplasmic reticulum, inhibiting T cell activation and affecting other Ca^{2+} signaling pathways. The lack of Ca^{2+} also prevents the NFAT production which controls the expression of the gene CD154. The activation of this gene is necessary in B cell activation (Schrezenmeier & Dörner, 2020). Finally, hydroxychloroquine also influences NOX inhibition which affects pro-inflammatory cytokines and nitric oxide availability, causing a reduction in ROS levels (Nirk et al., 2020).

Health impact

As an immunomodulatory drug, hydroxychloroquine has a good safety profile. The immune system pathways previously mentioned that are affected by this drug and not completely inhibited, stay largely conserved while the patient is undertaken the treatment. Hydroxychloroquine is not associated with risk of infectious conditions or cancer. However, usual side effects include gastrointestinal effects and severe adverse effects can lead to retinopathy. These effects can be reduced by taking the correct drug dosage (Schrezenmeier & Dörner, 2020).

Similarly, belimumab also have common gastrointestinal side effects such as diarrhea and nausea. Nevertheless, due to its immunosuppressive nature, this drug can increase the risk of infections, allergic reactions and hypersensitivity, and mental health problems. Belimumab can also promote progressive multifocal leukoencephalopathy (PML) and cancer. Therefore, it is highly important to use properly this drug and always under medical prescription as a treatment of SLE (Dennis, 2011).

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