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IMMUNOTHERAPY OF AUTOIMMUNE DISEASES (About 117 cases)

THESIS

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LIST OF ABBREVIATIONS

AAV : Anti-neutrophil cytoplasmic antibody (ANCA)-Associated Vasculitis
ADCC : Antibody-Dependent Cell-mediated Cytotoxicity
AIRE : The Autoimmune Regulator Gene
ANCA : Antineutrophil Cytoplasmic Autoantibody
BCR : B Cells Receptor
BD : Behçet's disease
CD : Cluster of Differentiation
CteC : Cortical Thymic Epithelial Cells
CTL : Cytotoxic T Lymphocytes
CTLA4 : Cytotoxic T-lymphocyte-Associated Protein 4
CYC : CYClophosphamide
DCs : Dendritic Cells
EGPA : Eosinophilic Granulomatosis With Polyangiitis
EULAR : European League Against Rheumatism
Fez2 : Fasciculation and Elongation Protein zeta-2
FOXP3 : the Forkhead Box Protein 3
GPA : Granulomatosis with PolyanGiitis
IL : Interleukin
INF : Interferon
ISG :The International Study Group The International Criteria for Behçet's disease
ICBD : The International Criteria for Behçet's disease
LFA : Lymphocyte Function-associated Antigen
m TECs : Medullary Thymic Epithelial Cells
MHC : Major Histocompatibility Complex
MMF : Mycophenolate MoFetil
MPA : Microscopic Polyangiitis
MTX : Methothrexate
PAMPS : Pathogen-Associated Molecular Patterns
PRRs : Pattern-Recognition Receptors
RA : Rheumatic Arthritis
SLE : Systemic Lupus Erythematosus
TH : T Cells Helpers
TRAs : Tissue Restricted Antigens
Treg : Regulatory T Cells
VLA-4 : Alpha-4 Integrin

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INTRODUCTION

Autoimmune diseases are a significant clinical problem because of their chronic nature, the associated healthcare cost, and their prevalence in young populations during the prime of their working and peak reproductive years.

Tackling these diseases at their source will require an understanding of how the abnormal immune reactions arise, how they are sustained, and the intrinsic mechanisms used to suppress these responses in healthy individuals

autoimmunity is defined as failure of an organism to recognize its own healthy tissue as self, and includes any immune response to the host's own tissue, whether it is humoral or cellular.

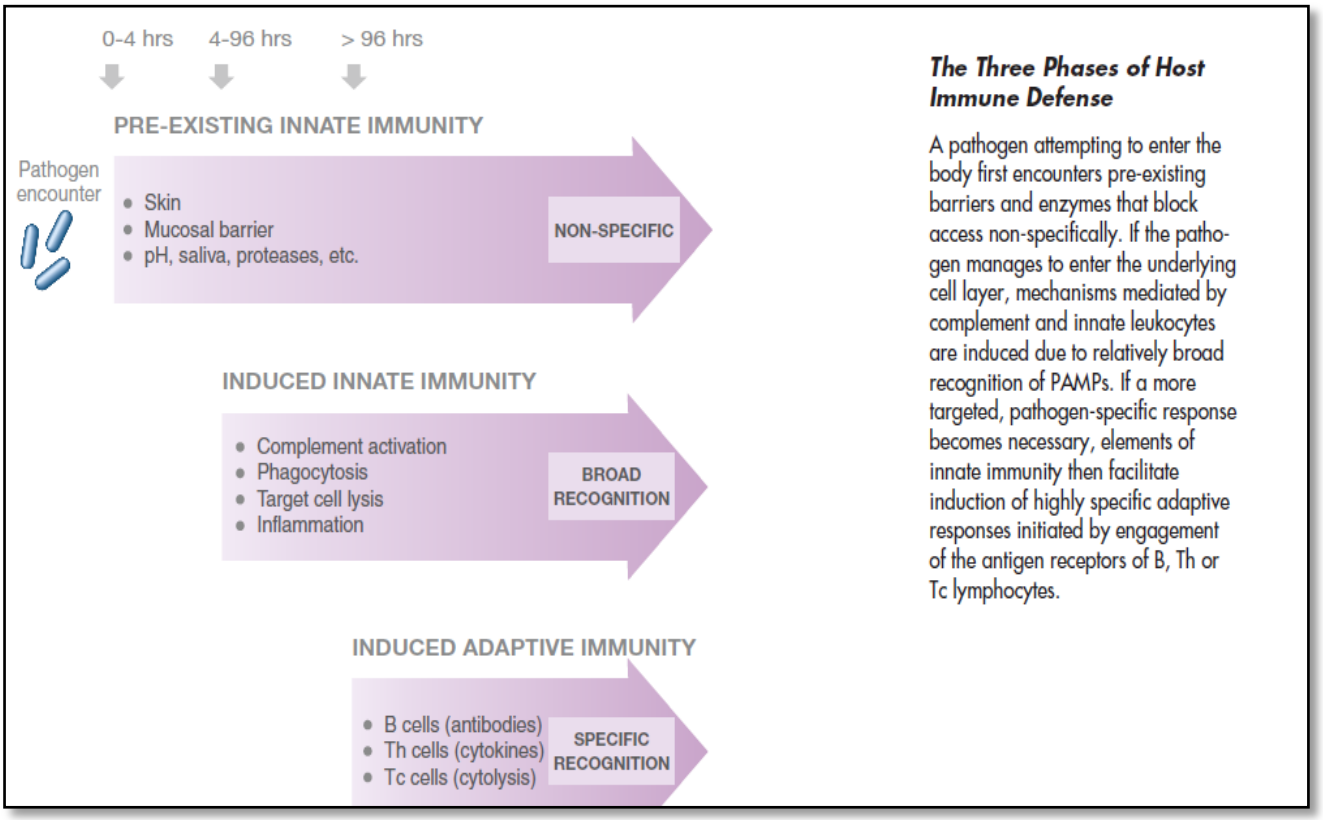
Autoimmune diseases are various group of disease , over 80 diseases , that share the characteristic of resulting from an immune response to auto-antigens during which the adaptative immune system , auto-reactive T-cells and B cells , release an specific immune reaction against self-antigens leading to tissue damages and malfunction .

The therapeutic tools of those diseases has known a great development, by the use of cytokine antagonist, that shown a great promise in their therapy. However, most of these therapeutic agents target the terminal phase of inflammation and do not address the fundamental problem that are responsible for the initiation and progression of autoimmune diseases.

Our objectives are to overview the latest understanding of the mechanisms that underlies autoimmune diseases, and mainly to present the immunotherapeutic tools and their molecular targets . in addition to highlight the experience of the department of internal medicine in CHU HASSAN 2 fez through a retrospective study of patients that were undergoing immunotherapy for their autoimmune disease, taking as example of study vacuities, in the department of internal medicine .

I. IMMUNE RESPONSE

The human body strives to maintain its homeostasis which can be referred to as a state of balance of the body's organs and its nervous and circulatory system. If this homeostasis is disturbed by a trauma , pathogen or dysregulation of the body cells than the immune system is called into play in order to restore the balance.[1] [1]



In a general view we can identify two essential functions of the immune system : first of which is identifying and eliminating invader pathogens (virus , bacteria , parasite) , second is cleaning the damage and dying cells of the organisms .This immune system refers to a collection of cells and proteins that function to protect the organism from foreign antigens, such as microbes (organisms such as bacteria, fungi, and parasites), viruses, cancer cells, and toxins.[2][2]

The immune system generates types of immunity: innate immunity and specific immunity , that are working in synergy and interconnected to each other(Figure1).

Figure 1: phases of the immune response. [1]

II. AUTOIMMUNITY

Tolerance is assured by two main processes, central tolerance and peripheral tolerance.

In both central and peripheral tolerance if a lymphocyte expresses self reactive receptor , four cellular strategies are deployed to deal with them[3][3]: clonal deletion; receptor internalization and edition; anergy and regulation.

1. Central Tolerance:

Central tolerance is induced at the primary sites of lymphocyte development ''the bone marrow for a developing B cell and the thymus for a developing T cell '' and it encompasses all of the mechanisms by which antigen-receptor recognition of self-antigen at these sites results in self-tolerance[4] [5].[4;5]

1.1 T cell tolerance

T cells achieve their maturation in the thymus, by two different processes: first a positive selection then a negative selection, that occur in different areas in the thymus[6] (Figure3).[5]

Positive selection allows only a restricted MHC selection for T cells, which indicates that only cells expressing TCR that are capable of interacting with self MHC molecules survive while those who can't die[7].[6]

The negative selection shapes the T-cell repertoire to avoid self-reactivity, which powerfully contributes to the avoidance of autoimmunity. This negative selection in the thymus functions as the major mechanism of central immune tolerance. In both selection processes the MHC -TCR interaction is the major determinant of cell fate[7] [8].

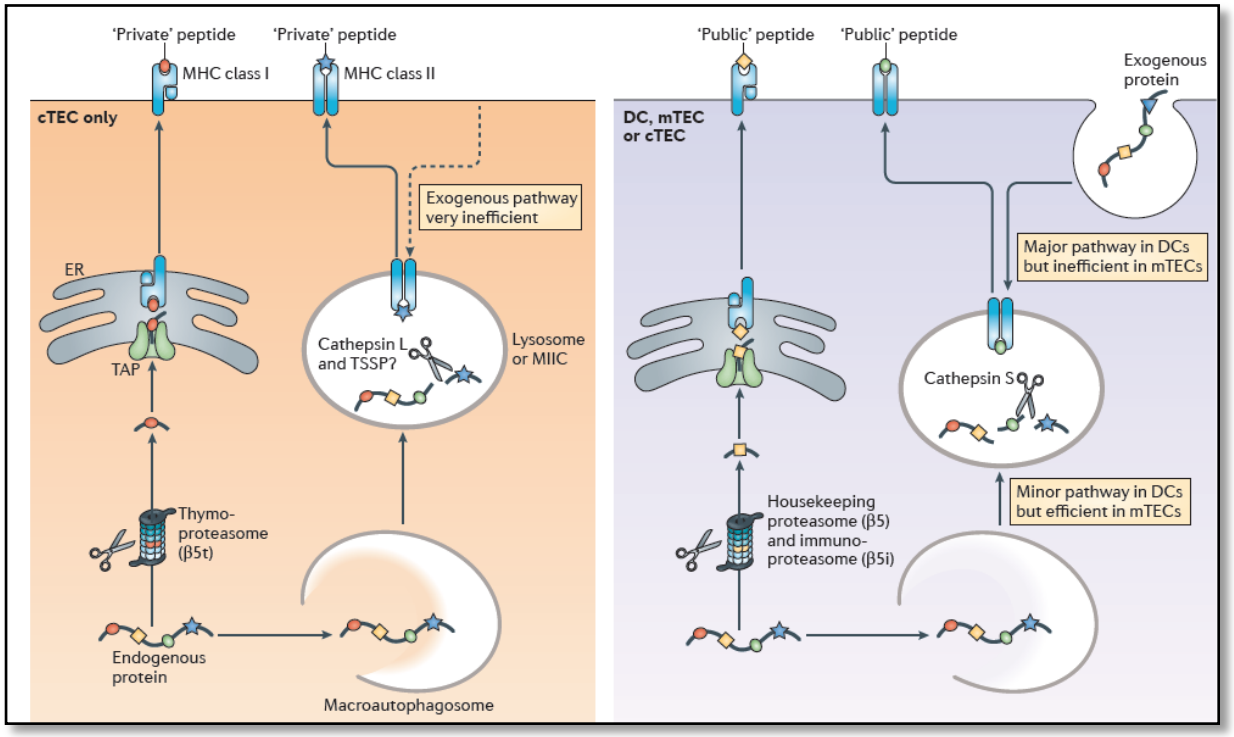


Figure 2: the unique machineries that these cells use to process ;antigens 7

The cTEC are the majors cells that conduct positive selection in the cortical thymus , thanks to a very specific machinery permitting them not only to produce self peptide MHC molecule , but to generate a unique repertoire of peptide that only expressed by these cells.

The medulla plays a crucial function for t cells tolerance, through transcription factors : AIRE and Fez2 that control The promiscuous gene expression of many tissue restricted antigens by epithelial medulla tymocyte and dendritic cells[9 6].[9;6]

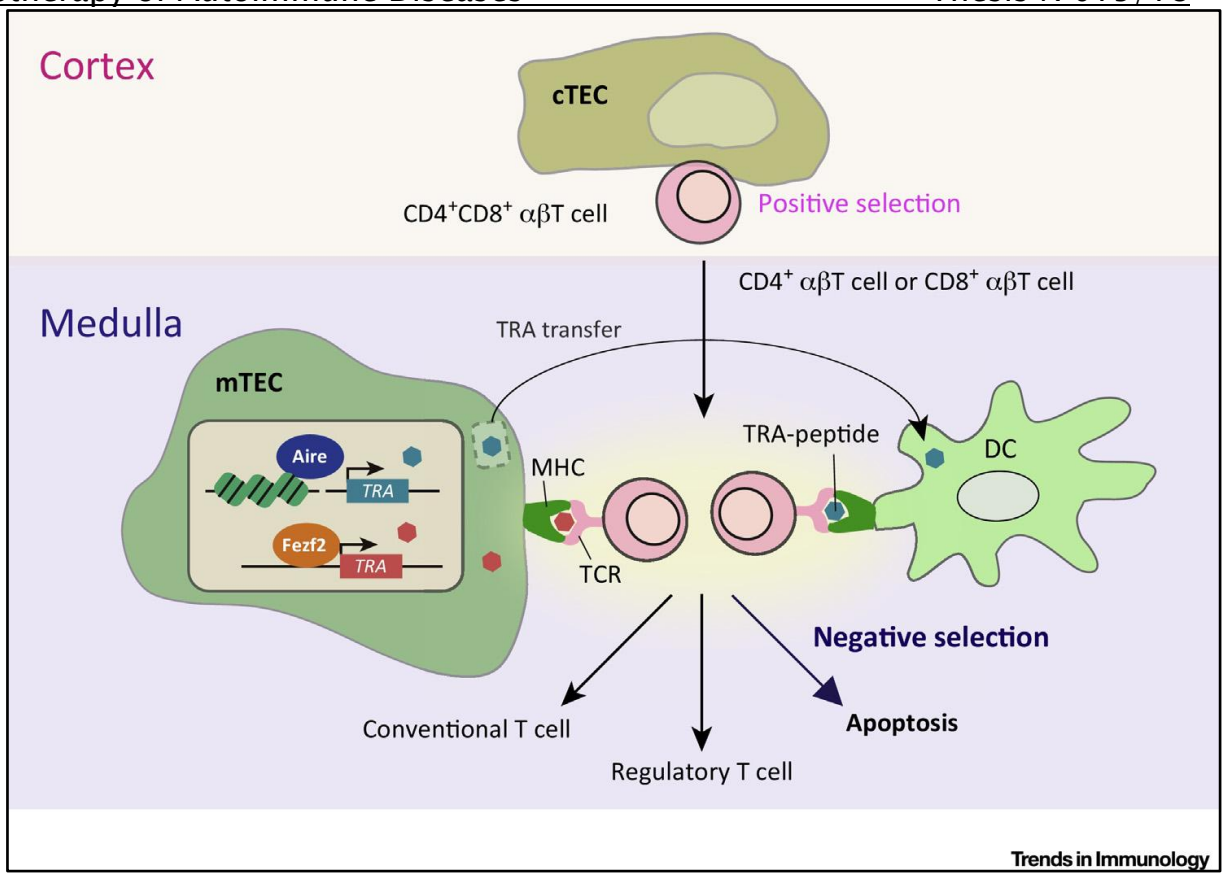


Figure 3: Schematic Diagram of T Cell Selection and TRA Expression in the Thymus 9.[9]

Thymocyte progenitors derived from bone marrow migrate into the cortex, and interact with cortical thymic epithelial cells(c TECs). Thymocytes express T cell receptors(TCRs) with CD4 and CD8, and interact with self-peptide-major histocompatibility complex (MHC) molecule complexes. They differentiate into CD4-orCD8-single-positive T cells(positive selection).CD4 T cells and CD8 T cells migrate into the thymic medulla, and interact with medullary thymic epithelial cells(m TECs) ,which present the peptide of tissue restricted antigen(TRA) in the context of MHC. Most autoreactive T cells are eliminated by apoptosis (negative selection), but some differentiate into regulatory T cells(agonist selection).TRA expression is controlled by transcriptional regulators such as Aire and Fezf2 in the mTEC.TRA genes are induced by Aire interacting with histone H3 or directly regulated by Fezf2. TRAs expressed by m TEC are taken up by the dendritic cells(DCs), which also contribute to the TRA presentation to T cells.

1.2 B cell central tolerance :

The BCR is exposed to auto-antigens in the bone marrow .Central B-cell tolerance is the process that negatively selects newly generated immature B cells that react with a self-antigen in the bone marrow environment. This is considered as the first checkpoint of B-cell tolerance[10].[10]

Therefore cells expressing self reactive BCR receptors can undergo three different fates, cell death by apoptosis, the production of a new receptor by receptor editing and ignorance (Figure 4) [11].[11]

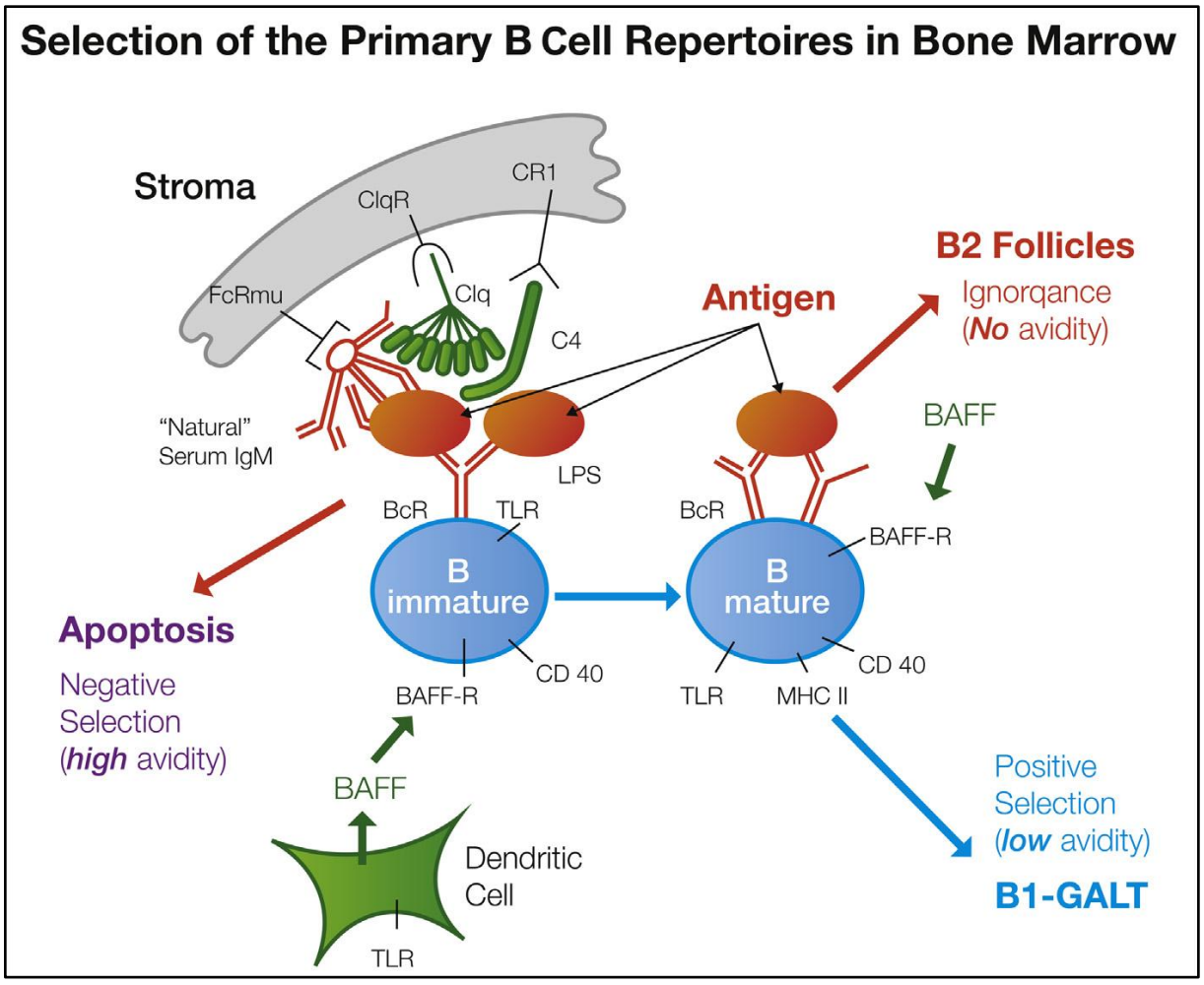


Figure 4: selection of B cells in bone marrow[12].[12]

2. peripheral tolerance :

Peripheral tolerance represents an essential mechanism by which the immune system obtains tolerance (Figure 5)[13].[13]

To have a peripheral checkpoint is essential for tolerance for many reasons [14] [14] :

- Self reactive BCR can also be generated at the secondary lymphoid organs through somatic hyper mutation[15]. [15]
- Low-avidity auto-reactive T cells, as well as T cells bearing TCRs having high avidity for Tissue Restricted antigens that are not expressed in sufficient amounts in medullar thymic epithelial cells circulate in the periphery and are exposed to self antigens. [14]

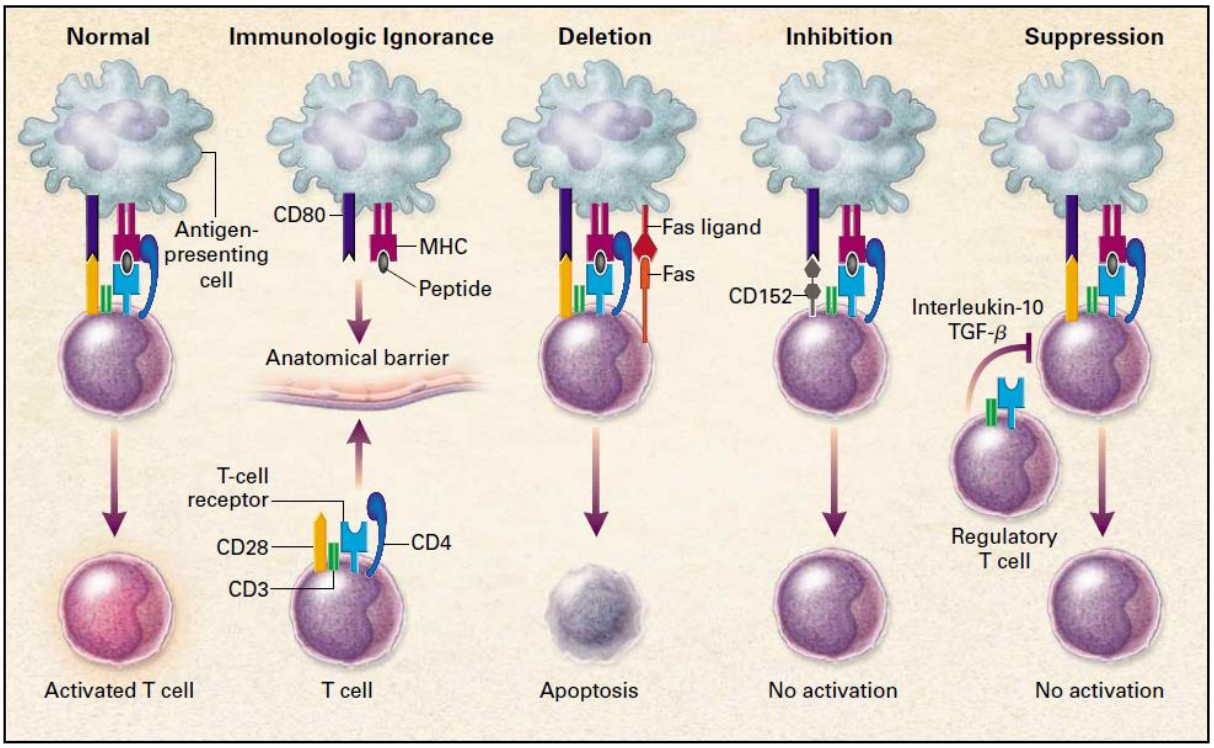


Figure 5: Peripheral Mechanisms of the Induction of Tolerance. [13

T cells that are physically separated from their specific antigen — for example, by the blood-brain barrier — cannot become activated, a circumstance referred to as immunologic ignorance. T cells that express the Fas (CD95) molecule on their surface can receive their signals from cells that express Fas ligand and undergo apoptosis, a process known as deletion. One example of inhibition is as follows: CD152 binds CD80 on antigen-presenting cells, thereby inhibiting the activation of T cells. Regulatory T cells c an inhibit, or suppress, other T cells, most likely through the production of inhibitory cytokines such as interleukin-10 and transforming growth factor b(TGF- b).

2.1 Dendritic cells in peripheral tolerance :

Dendritic cells are known for being the most efficient antigen presenting cells, playing by that the role of intermediate between innate immunity and specific immunity [16]. [16]

In steady state, Dendritic cells typically present an immature phenotype characterized by low expression of MHC class II and co-stimulatory molecules, and they promote tolerance by inducing T-cell anergy, deletion, or generation of Regulatory T cells.

Maturation of Dendritic cells usually makes them immunogenic and co-stimulation pathways greatly influence the outcome of T-cell stimulation and play a central role in immune tolerance [17].[17]

2.2 Ignorance of self peptide -MHC complexes :

Physical separation of potentially auto reactive T cells from the parenchyma cells that express a Tissue Restricted Antigens is a barrier to self peptide MHC molecule recognition. This is possible due to the restricted trafficking patterns of naïve T cells [17] .[17]

2.3 Anergy and deletion :

Anergy refers to intrinsic biochemical changes in the cells displaying auto-reactive receptors, either by decreased display of self-reactive receptor on the cell surface, or by increasing of the threshold of cell activation[13].[13]

2.4 Regulatory T cells:

Regulatory T cells (T reg), play a pivotal role in the maintenance of peripheral immunological tolerance and the control of immune responses towards pathogens and tumors [18].[18]

Regulatory T cells fall into 2 groups :

- The first , CD25+CD4+ Regulatory T cells, develops in the thymus characterized by surface expression of CD4 and CD25 antigen and nuclear expression of the fork-head box protein 3 (FOXP3) transcription factor that is essential for their development and function(Figure 6) [19]. [19]

- The second group differentiate in the periphery from naïve CD4 T-cells , in response to stimulation with specific antigen .

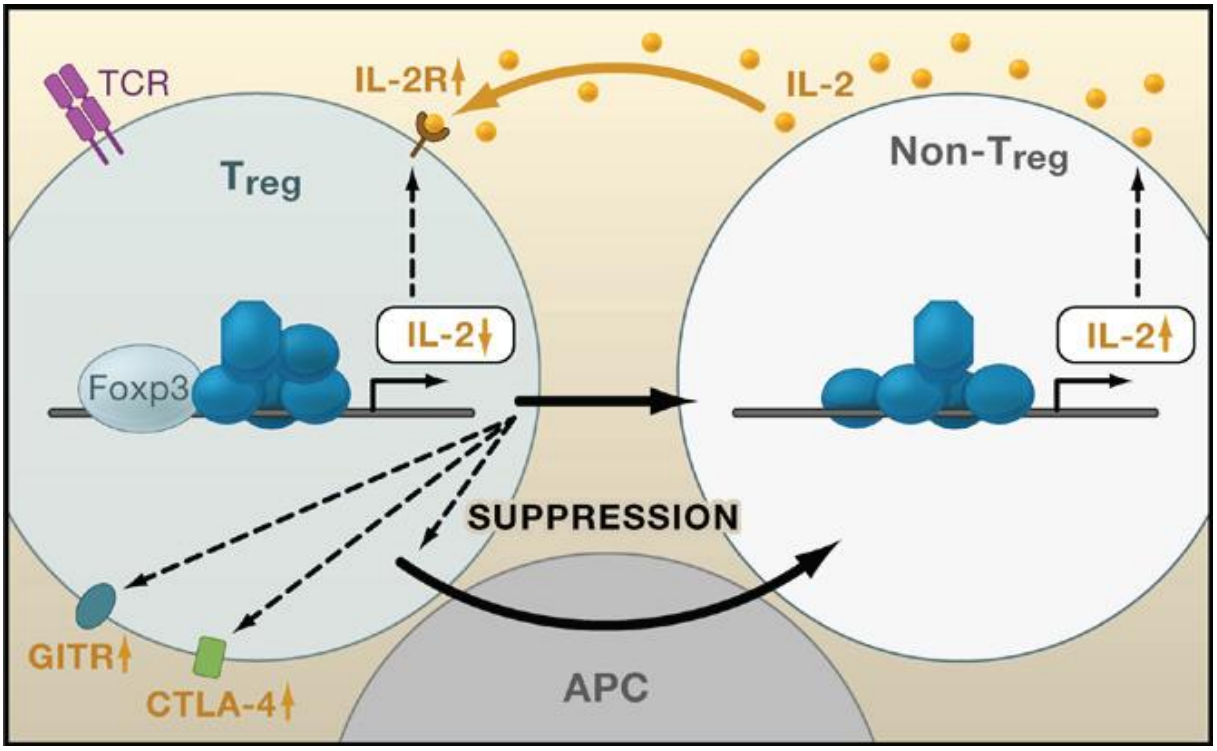


Figure 6: Key Roles of IL-2 in Immune Homeostasis[18]

Interactions among Tregs, non-Treg cells, and antigen-presenting cells (APC) and feedback control of Treg function via IL-2. Foxp3, together with other transcription factors and coactivators/corepressors, represses the transcription of IL-2 in Tregs, rendering them highly dependent on exogenous IL-2 (mainly produced by activated non-Treg cells) for their maintenance and function. Foxp3 also activates the genes encoding Treg-associated molecules such as CD25, CTLA-4, and GITR and confers suppressive activity to Tregs, which directly suppress non-Treg cells or modulate the function of APC to activate non-Treg cells.[18]

Regulatory T cells use four mechanisms (inhibitory cytokines, cytolysis, metabolic disruption and modulation of APC function) to control the response of peripheral T cells to self-MHC complexes, the failure to do so leads to fatal autoimmunity (Figure7)[20]. [20]

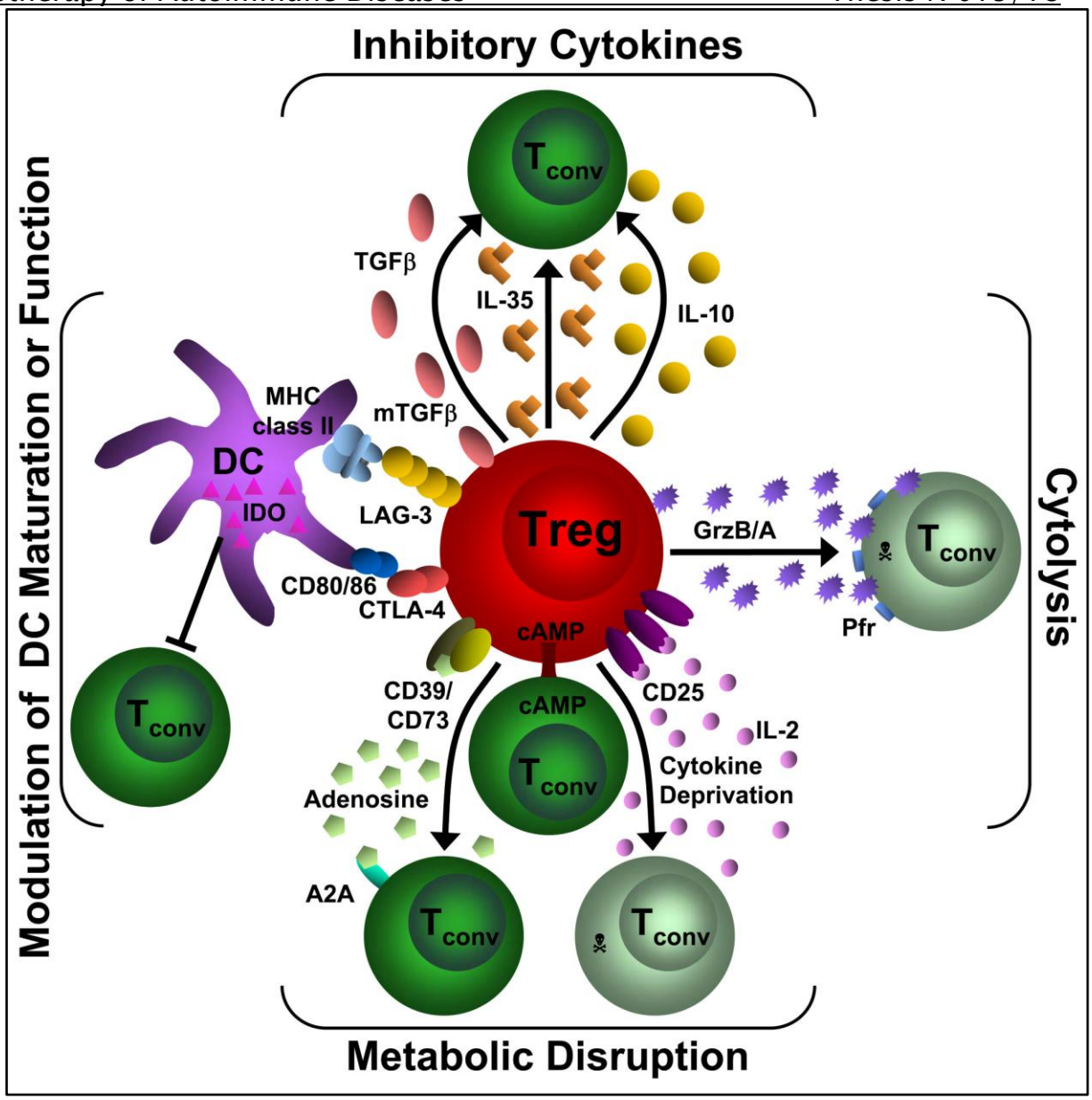


Figure 7: Mechanisms of Treg suppression.[20]

This diagram depicts the four basic modes of Treg suppression. A primary mode of Treg suppression is mediated through the inhibitory cytokines IL-10, IL-35 and TGFβ. Tregs also induce cytolysis through granzyme A/B (GrzB/A) and perforin (Pfr). They can disrupt metabolic function by IL-2 deprivation which results in apoptosis, cAMP inhibition or by CD39/CD73-generated A2A-mediated immunosuppression. Tregs can also modulate DC maturation or function via a CD80/86 and CTLA-4 interaction or through a LAG-3 and MHC class II interaction. In addition, they can induce the upregulation of IDO in DCs.

T conv = conventional T cell; GrzB/A= granzyme B or A, Pfr = perforin , cAMP= cyclic adenosine monophosphate , A2A= adenosine-purinergic adenosine receptor, IDO= indoleamine 2,3-dioxygenase, DC= dendritic cell

2. Autoimmunity and autoimmune diseases : the barriers:

It is important to note however that even under the strict vigilance of central and peripheral tolerance, small numbers of potentially self-reacting lymphocytes can still 'leak out' into the periphery. The existence of these potential self-reactive T and/or B lymphocytes, and/or the ability of these cells to produce auto-antibodies, does not necessarily lead to pathology. Accordingly, autoimmunity can sometimes be classified as 'physiological' and 'pathological' autoimmunity. Physiological autoimmunity is usually transient without evidence of clinical disease. This is exemplified by the presence of so called natural auto-antibodies, which help eliminate degraded self- and foreign antigens for maintenance of homeostasis[21].[21]

The pathological response leading to auto-immune disease requires the combination of predisposition factors allowing an immune response against self-antigens that results in the damage and eventual dysfunction of target organs (Figure 8) [22]. [22]

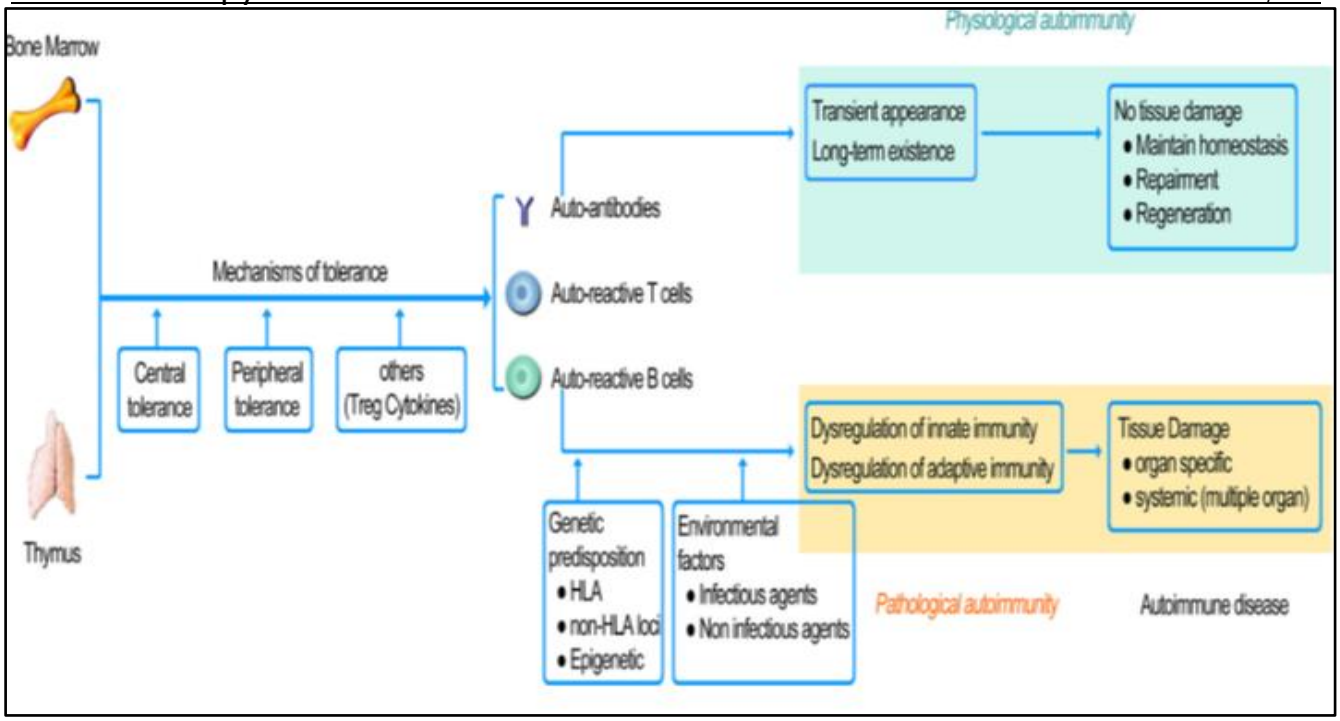


Figure 8: Autoimmunity and autoimmune diseases. [21]

III. AUTOIMMUNE DISEASES:

1. Introduction :

Autoimmune diseases are a group of over 80 diseases, characterized by an immune response directed towards auto-antigens and leading to tissue damage and malfunction.

All autoimmune diseases are believed to go through sequential phases (Figue10) : initiation, progression and resolution.[21]

Autoimmune diseases are multi-factorial depending on hereditary and environmental factors (Figure 9). They generally result from the association of environmental initiating factors and the presence of a genetic predisposition.The consequence is the disruption of the immune system and the lost of self tolerance, causing a clinical manifestation throw immunological tissue damage[23]. [23]

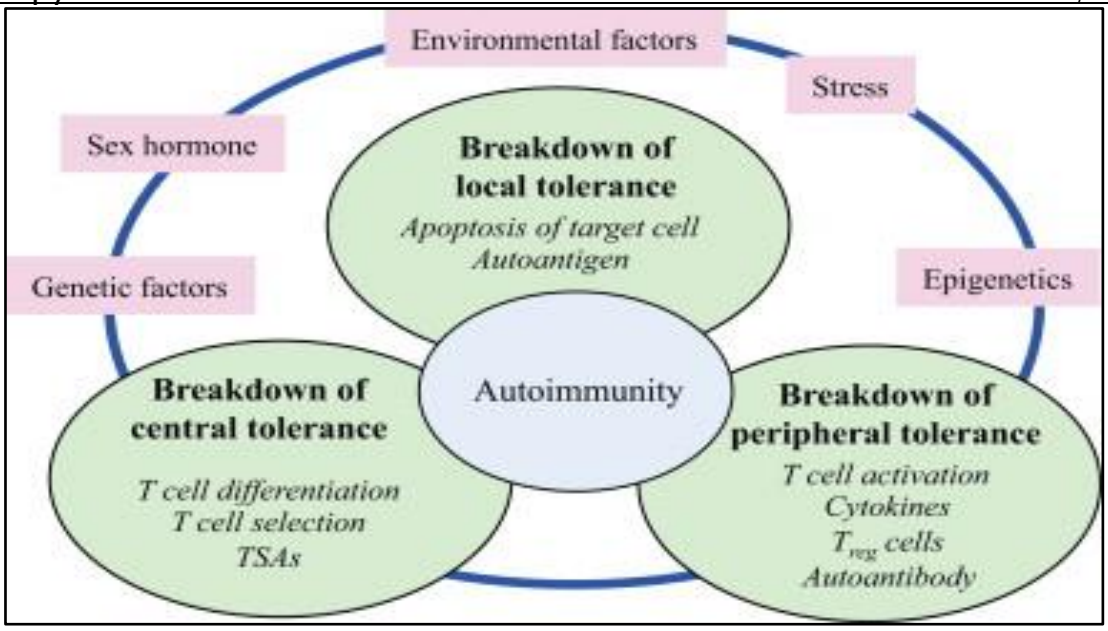


Figure 9: Predispoition factors of autoimmune diseases.[21]

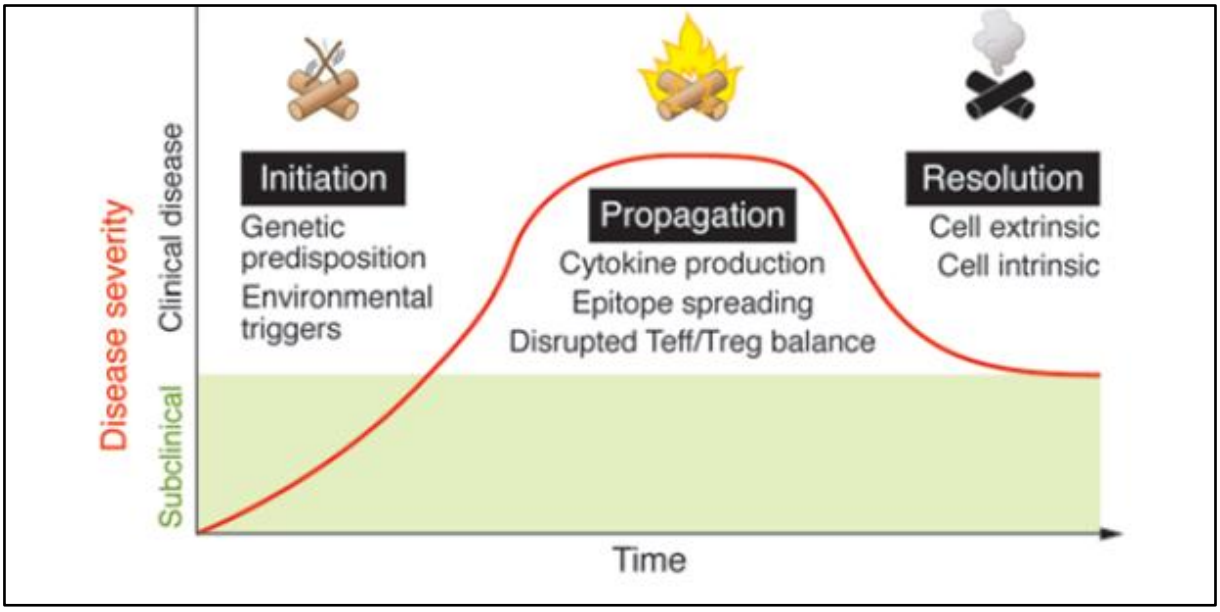


Figure 10: Phase of autoimune diseases.[21]

2. Predisposition factors:

Several studies have determined many susceptibility genes and environmental factors that are the key risk factors which lead to loss of tolerance [22]. [22]

2.1 Genetics factors :

Clinical reports state that patients often described a family history of the same or related autoimmune disease. For instance, patients diagnosed with Graves' disease and

Hashimoto's thyroiditis may have a family history of one or the other of these diseases. While there are few monogenic autoimmune diseases, the vast majority of autoimmune diseases are related to multiple susceptibility loci [21].[21;26]

2.1.1 Single Gene Defects associated with Autoimmunity:

- Autoimmune polyendocrinopathy syndrome type 1 is related to A mutation in the autoimmune regulator (AIRE) gene Affecting negative selection[24] .[24]
- The immune dysregulation poly-endocrinopathy enteropathy X-linked syndrome (IPEX) (in which there is a defect in the Foxp3 gene, localized to Xp11.23) and IL-2Ra deficiency (in which there is a deletion of the CD25 gene); in both cases, these mutations alter the functional development of CD4+CD25+ regulatory T cells , leading to loss of peripheral tolerance [25] [12].[25 ;12]
- Autoimmune lympho-proliferative syndrome (ALPS) characterized by an excess of T and B cells and by autoantibody production. This is secondary to a deficiency in FAS expression, knowing that FAS is involved in immune response down regulation by activating apoptosis of FAS expressing- cells [26].[26]

2.1.2 Multiple Gene Loci that are Associated with Autoimmunity:

Most autoimmune diseases are multigenic, with multiple susceptibility genes working in concert to produce the abnormal phenotype.[12;26]

HLA molecules : Many studies have shown an association between the major histo-compatibility complex (MHC) and human autoimmune diseases[27][28] .[27 ; 28]

2.2 Environmental factors:

A number of environmental factors, both infectious as well as non infectious, have been shown to play an important role in the onset of diseases in genetically predisposed individuals[21] [22]. [21;.22]

These environmental factors include nutrition, the microbiota, infectious processes and xenobiotics, such as tobacco smoke, pharmaceutical agents, hormones, ultraviolet light,

silica solvents, heavy metals, vaccines and collagen/silicone implants. They may have various roles in promoting, causing or modifying autoimmune diseases.[21]

2.2.1 Infectious Agents :

Infectious agents have long been the most well studied environmental factors. The best example of a relationship between infection and immunity is acute rheumatic fever, which occurs following exposure in genetically susceptible hosts to *Streptococcus pyogenes*. They initiate auto-reactivity through molecular mimicry polyclonal activation, or the release of previously sequestered antigens[29] (Figure 11).[29.30]

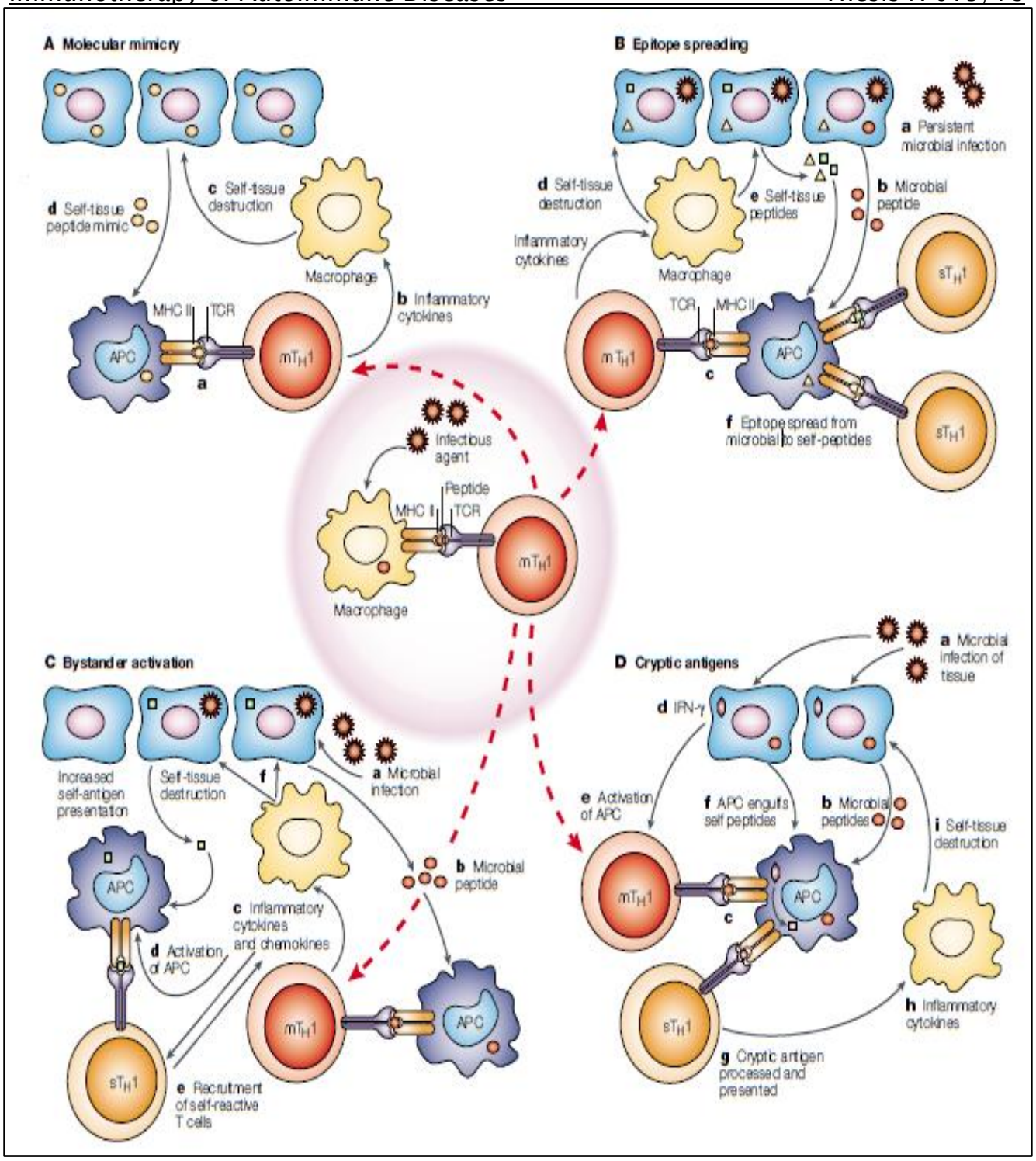


Figure 11: Mechanisms of infection-induced autoimmunity[30].[30]

After a microbial infection, activated microbe-specific TH1 (mTH1) cells migrate to the infected organ. A | Molecular mimicry describes the activation of crossreactive TH1 cells that recognize both the microbial epitope (mTH1) and the self epitope (sTH1) (a). Activation of the crossreactive T cells results in the release of cytokines and chemokines (b) that recruit and activate monocytes and macrophages, which mediate self-tissue damage (c). The subsequent

release of self-tissue antigens and their uptake by APCs perpetuates the autoimmune disease (d). B | Epitope spreading involves a persistent microbial infection (a) that causes the activation of microorganism-specific TH1 cells (b,c), which mediate self-tissue damage (d). This results in the release of self peptides (e), which are engulfed by APCs and presented to self-reactive TH1 cells (f). Continual damage and release of self peptides results in the spread of the self-reactive immune response to multiple self-epitopes (f). C | Bystander activation is the nonspecific activation of self-reactive TH1 cells. Activation of microorganism-specific TH1 cells (a,b) leads to inflammation (c,d) and results in the increased infiltration of T cells at the site of infection and the activation of self-reactive TH1 cells by TCR-dependent and -independent mechanisms (e) Self-reactive T cells activated in this manner mediate self-tissue damage and perpetuate the autoimmune response (f). D | Cryptic antigen model describing the initiation of autoimmunity by differential processing of self peptides. Following microbial infection (a) IFN-γ is secreted by both activated microbe-specific TH1 cells (b,c) and microbe-infected tissue cells (d). This activates APCs (e) and can lead to APC engulfing self-antigens (f). Cytokine activation of APCs can induce increased protease production and different processing of captured self-antigens, resulting in presentation of cryptic epitopes. The presentation of these cryptic epitopes can activate self-reactive TH1 cells (g), leading to self-tissue destruction (h,i). APC, antigen-presenting cell; MHC II, major histocompatibility complex class II; *TCR, T-cell receptor.*

2.2.2 Non infectious agents:

Many factors were found to alter the immune system and interfere with its function. The best example of noninfectious environmental agents is the relationship between gluten

ingestion and celiac disease. However, perhaps of more interest is the appearance of autoimmune diseases following exposure to many common pharmaceutical agents, for example many drugs can induce lupus[12].

Vaccination is a long established and extremely important public health measure, and fortunately, side effects are rare. However, for genetically predisposed individuals, there are rare instances of autoimmune reactions and autoimmune disease that have been precipitated by vaccines, likely via the mechanisms of molecular mimicry. This should not, however, prevent the use of vaccination.

It is not obvious whether vaccination can exacerbate autoimmune disease and it is recommended to avoid vaccination during an active phase of autoimmunity.[12]

It has long been known that vitamin D is a natural immune modulator, Epidemiological studies have demonstrated that reduced levels of vitamin D lead to an increased risk for loss of tolerance. In fact, reduced levels of vitamin D have been demonstrated in multiple human autoimmune diseases exposure[22].[22;12]

Smoking is by far the most well-recognized risk factor for rheumatic arthritis as well as for Systemic lupus erythematosus . It might contribute to disease development via several pathways. Tobacco smoke contains several Toll Like Receptors stimulating compounds, including lipopolysaccharide (a TLR4 agonist), which can elicit an innate immune response. By interacting with the HLA haplotype and changing gene expression in the joint, smoking may promote the development of RA [12] [21].[12;21]

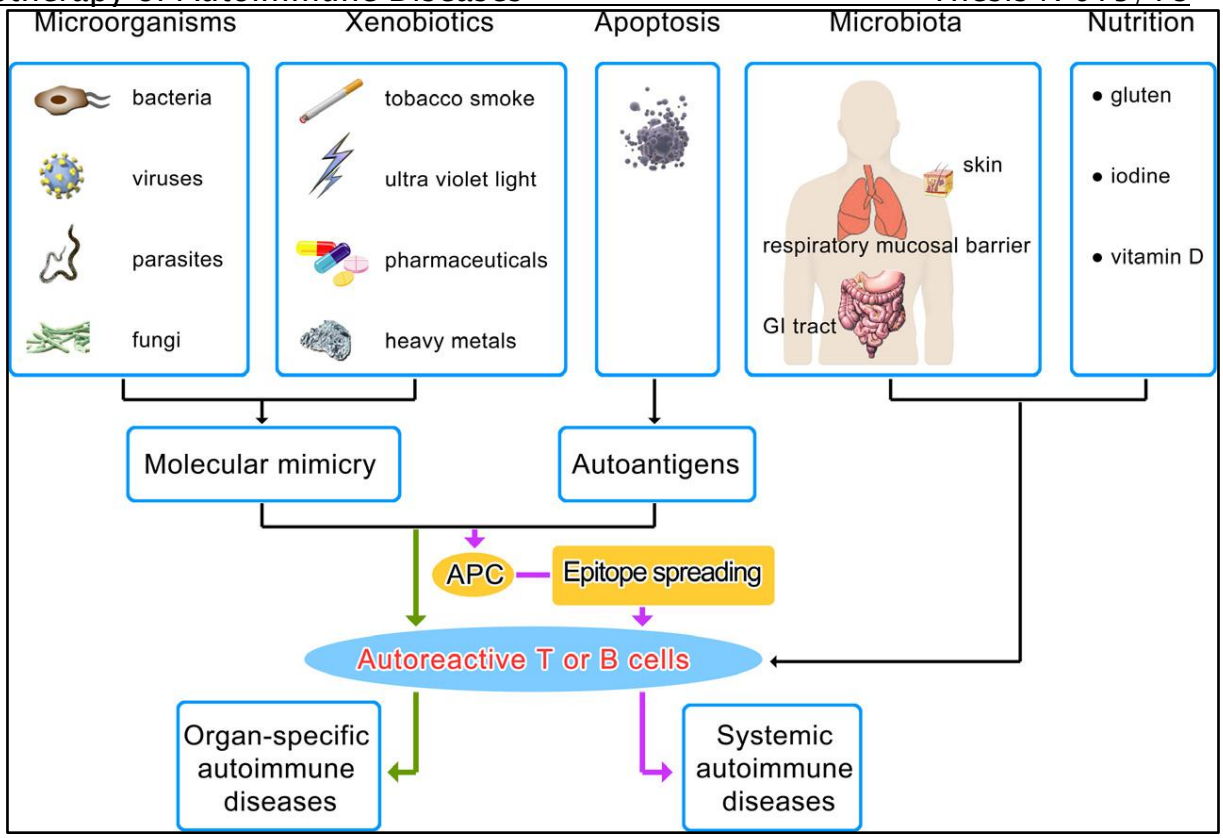


Figure 12: Predisposition factors for Autoimmune diseases.[21]

3. The break of tolerance mechanisms:

General Mechanisms of autoimmunity: In the initiation of an autoimmune response, one of the following events may be involved[31].[21;31]

3.1 Sequestered antigen release reaction:

This reaction involves the stimulation of competent T-cells and/or B-cells by sequestered self-antigens.

Sequestered antigens such as sperm antigens and lens proteins are not available and accessible to the normal immune cells. Therefore, no self-tolerance develops to these antigens. Such antigens may induce an autoimmune reaction when they are released into the immune system, by tissue injury[25]. [21; 25]

3.2 Loss of suppressor activity :

Normally, the presence of a suppressor T-cell may block a self antigen triggering of a T-cell helper signal. The suppressor T-cells may also block and inhibit modification of the competent B-cells to produce autoantibody.[25]

3.3 Molecular mimicry :

Molecular mimicry is one of the pathogenic mechanisms for infectious induced autoimmune disease .The linear amino acid sequence or conformational structure may be similar and shared by the molecules of different origins.[25]

The origin of the molecules are often from a virus or bacteria which show a similar structure with a normal host self-determinant in cases of autoimmunity [29] (Figure 13).[29]

A classic example of molecular mimicry is post-streptococcal rheumatic fever. Epidemiologic and clinical evidence associates beta-hemolytic streptococcal infections with acute rheumatic fever and heart disease. [25]

3.4 T-cell bypass mechanism:

A non tolerant immune-competent B-cell can be stimulated to produce autoantibody without the need for an immunocompetent specific T-cell. The B-cells may be stimulated by two general pathways:

- The auto-antigens or cross-reactive foreign antigens may form immunogenic units to simulate T-cell helper cell signals to stimulate immunocompetent B-cells. Helper determinants may be drugs, viruses, and bacteria.[31]
- polyclonal activation of B-cells ; The immunocompetent B-cells may be nonspecifically stimulated by viruses, adjuvant, or allogenic cells, initiating a graft versus host reaction to produce auto-antibodies.[21;21]
- T-cell bypass autoimmune reaction may be seen with drug administration, virus infection, adjuvant effect, bacterial infection, degradation and alteration of auto-antigens, and allogenic cells.[25]

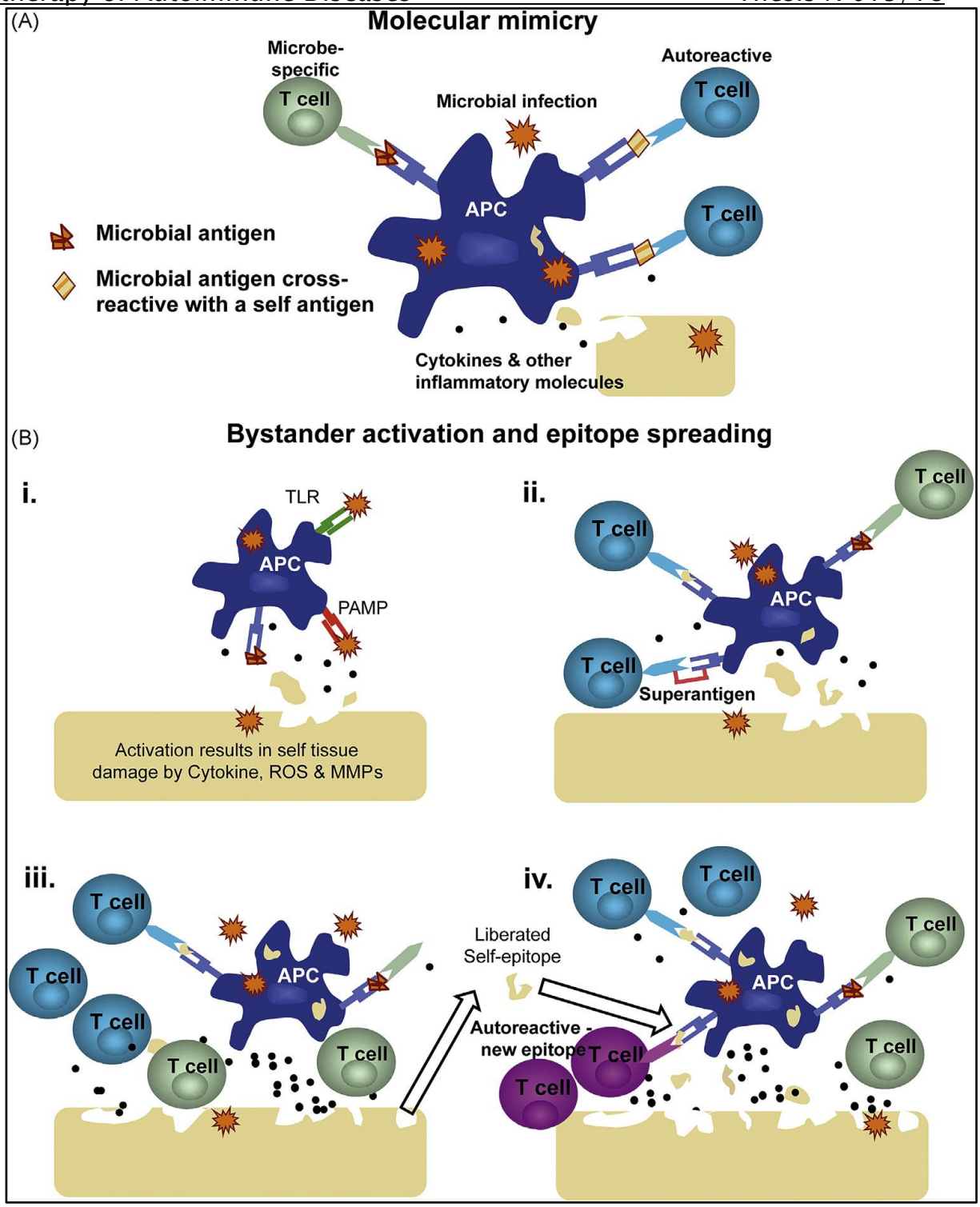


Figure 13: Molecular mimicracy and bystander activation[12][12]

4.The propagation:

Autoimmune diseases are typically characterized by a persistent inflammatory self recognition process that ultimately leads to chronic progressive disability. This chronic immune reaction, characterized by relapse and resolution[21] , is due to majors facts: the first one of is that AD is a self direct immune reaction , so the stimulator antigens is always present. The second is a phenomenon that leads to recruit additional self reactive lymphocytes : epitope spreading[30].[30]

Epitope spreading has been defined as a consequence of acute or persistent infection and secondary to chronic tissue destruction that occurs during progressive autoimmune disease. It is defined as a diversification of epitope specificity from a dominant epitope to subdominant (cryptic) epitopes (Figure 14).[30]

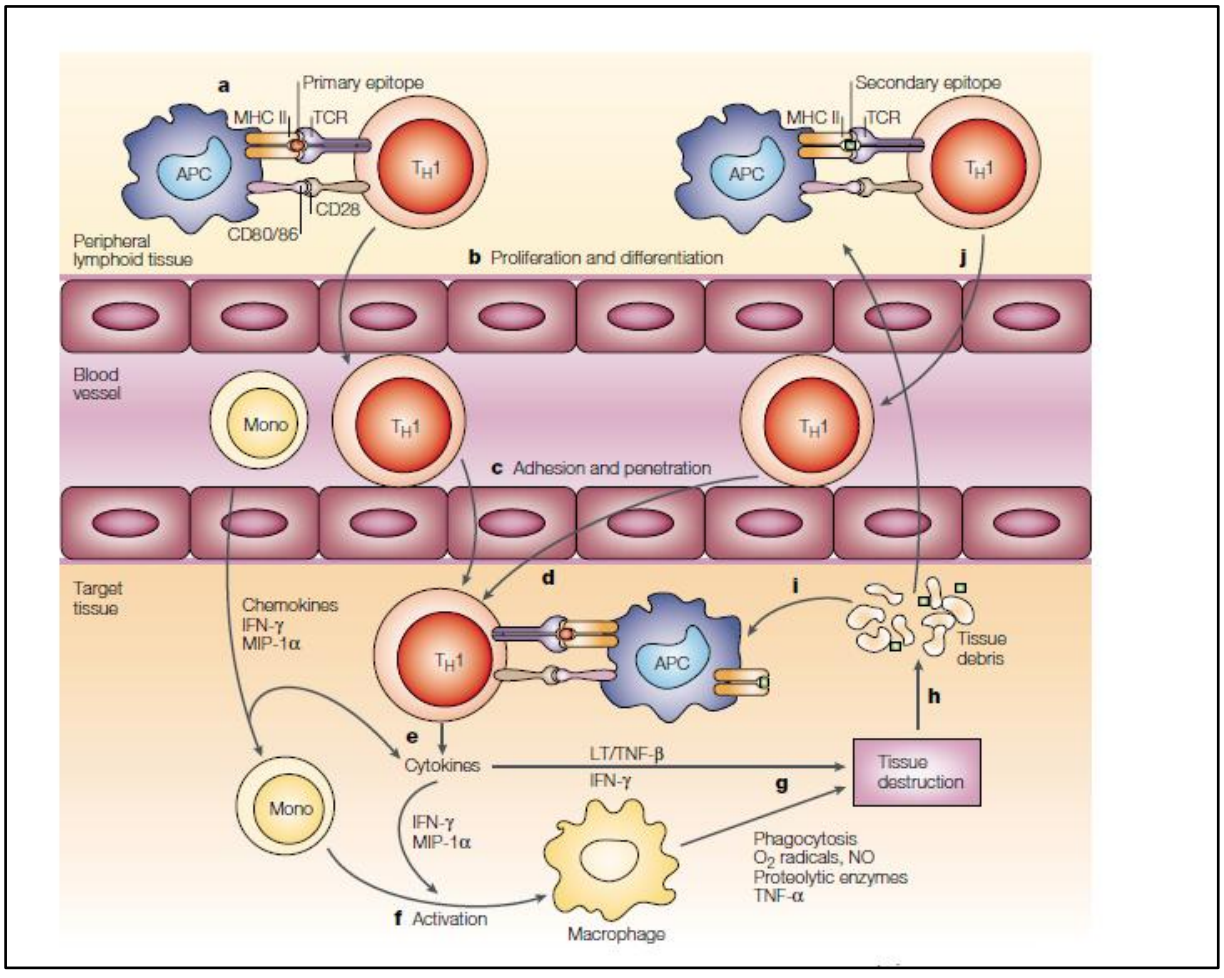


Figure 14: Epitope spreading in autoimmune and virus-induced tissue immunopathology.[30]

Presentation of the primary epitope (the immunodominant self or viral epitope) occurs in peripheral lymphoid tissue , resulting in activation and differentiation of autoreactive TH1 cells . The activated TH1 cells migrate into the target tissue, where they encounter antigen presented by resident APCs.. After antigen restimulation, the pathologic TH1 cells release a cascade of chemokines and cytokines , leading to recruitment of additional mononuclear phagocytes from the peripheral blood, which are activated along with resident APCs . Activated mononuclear cells then lead to bystander tissue destruction via phagocytic mechanisms and release of TNF, proteolytic enzymes, NO and O2 radicals. The tissue debris is processed and presented on resident and peripheral APCs , leading to the activation and differentiation of a second wave of TH1 cells , which can re-enter the tissue and cause additional tissue destruction.

5. Mechanisms of tissue injury:

When immune tolerance is broken, auto-antibodies and self-reactive lymphocytes are produced leading to classical or pathological autoimmunity sometimes associated with tissue damage. [19;12]

Tissue destruction can be divided into a variety of effectors pathways depending on the autoimmune disease (Figure18). The immune system is promiscuous and there is often an orchestrated response that involves a multitude of diverse cell populations. This has made treatment of some diseases, such as Systemic lupus erythematosus very difficult. [32]

5.1 Auto-antibodies:

The presence of auto-antibodies is a common feature of autoimmune diseases, and a large number of serum antibodies are directed against functional structures of the cell (nucleic acids, nuclear molecules, receptors or other functional cell components).They play a central role in diagnosis and classification and are involved in tissue damage[32]. [32;53]

5.1.1 ADCC (antibody dependent cellular cytotoxicity) :

Classical ADCC is mediated by natural killer cells that carry the receptor for the Fc portion of IgG; binding stimulates the release of hydrogen peroxide and hydroxyl radicals. Other cells, such as monocytes and eosinophils, can also mediate ADCC. ADCC is a known mechanism in Autoimmune Tissue Destruction mediated by antithyroperoxidase antibodie.[12;32]

5.1.2 Immune complexes :

Systemic lupus erythematosus is a typical example of damage by immune complex. In rheumatic arthritis, rheumatoid factor–IgG complexes are involved in synovial damage. Auto-antibodies may also interact with cell surface receptors, which can both activate (anti-thyroid-stimulating hormone for Graves' disease) and block selective pathways (anti-acetylcholine receptor for myasthenia gravis) [33](Figure15). [21;33]

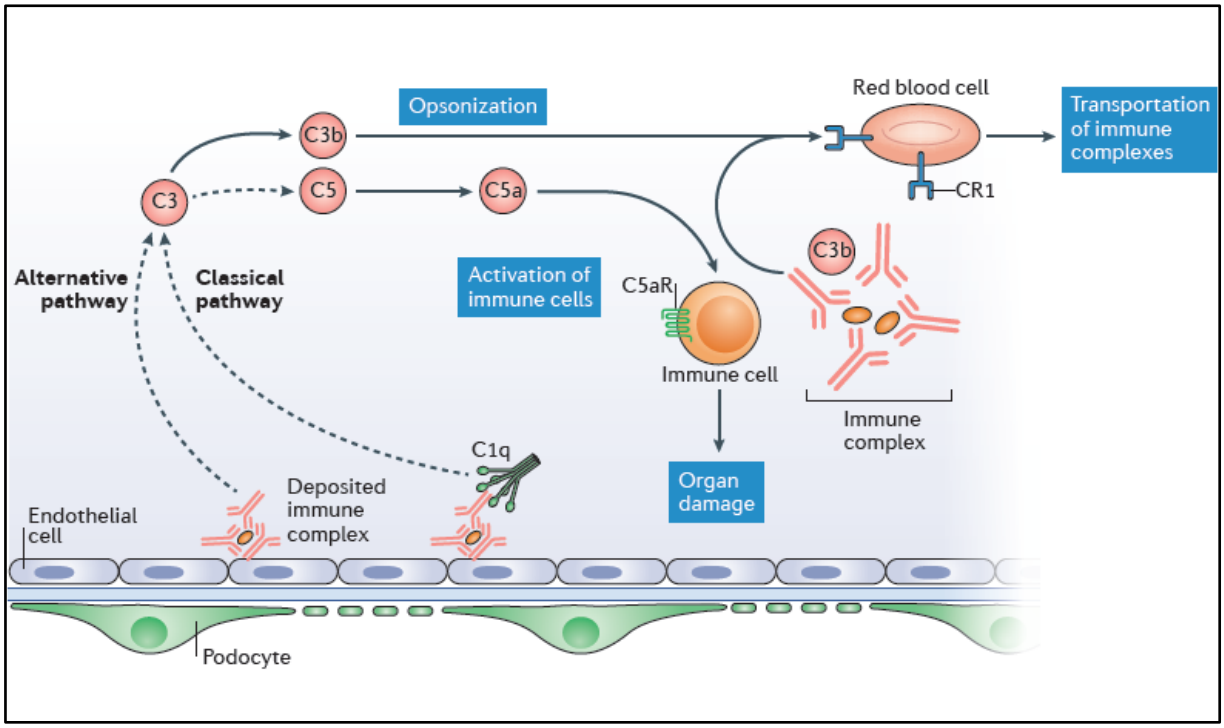


Figure 15: Schematic overview of complement activation by immune complexe [33]

5.1.3 Anti-receptors auto-antibodies :

This mechanism includes binding to extracellular molecules, such as the anti-phospholipid antibody syndrome, where auto-antibodies are directed against α 2 glycoprotein I in plasma (figure16).[33]

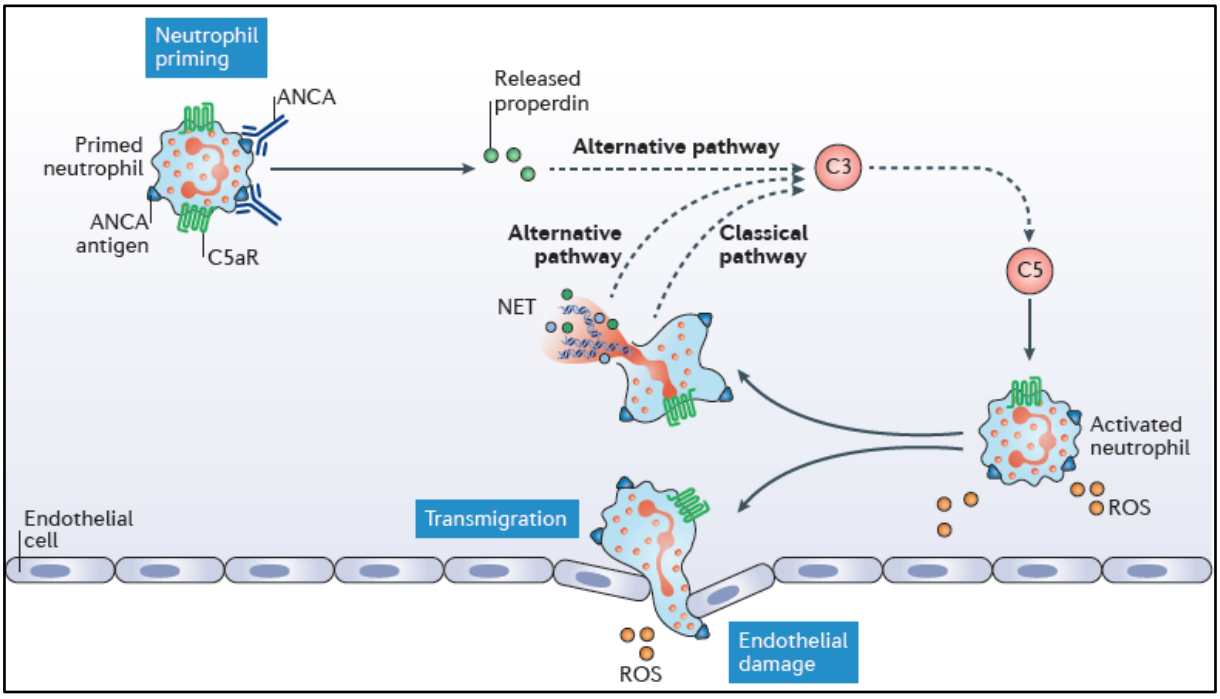


Figure 16: Schematic overview of complement activation in anti-neutrophil cytoplasmic antibody (ANCA)-associate vasculitis[33]

5.2 Autoreactive T cells :

Auto-reactive cytotoxic T lymphocytes (CTL) recognize a target cell by binding the T-cell receptor (TCR) to the appropriate combination of MHC I and auto-antigen-derived peptides. Then, a complex of MHC I and auto-antigen- derived peptides directly kills target cells through different mechanisms: secretion of cytotoxic granules (perforin and granzyme B) (figure 17), resulting in disintegration of the cell membrane and induced apoptosis, activation of Fas-Fas ligand, which induces apoptosis; and release of cytokines (such as TNF-a and interferon-c), leading to tissue injury .[12;21]

The paradigm of Th1/Th2 balance has shifted due to the increasing body of information on other CD4 subsets, including Th17 Tregs and T follicular helper cells (Tfh) . [21]

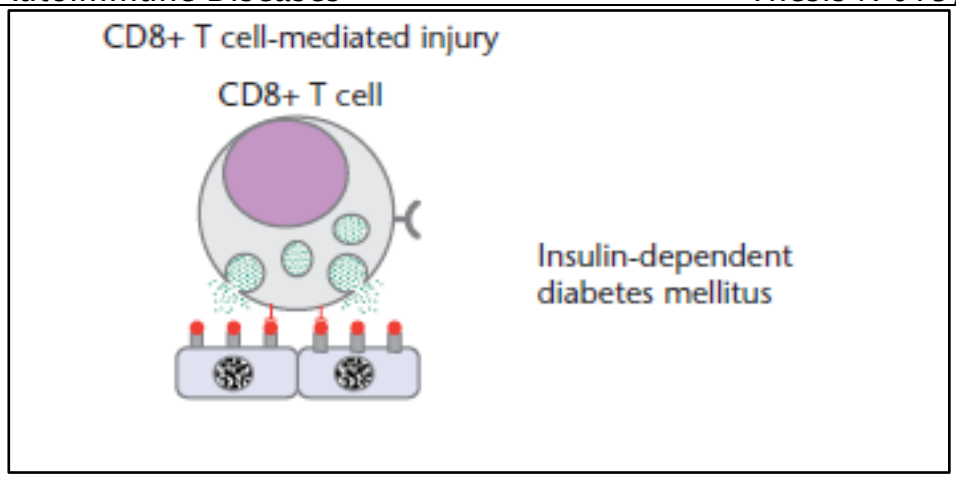


Figure 17: schematic presentation of cells mediated autoimmunity.[53]

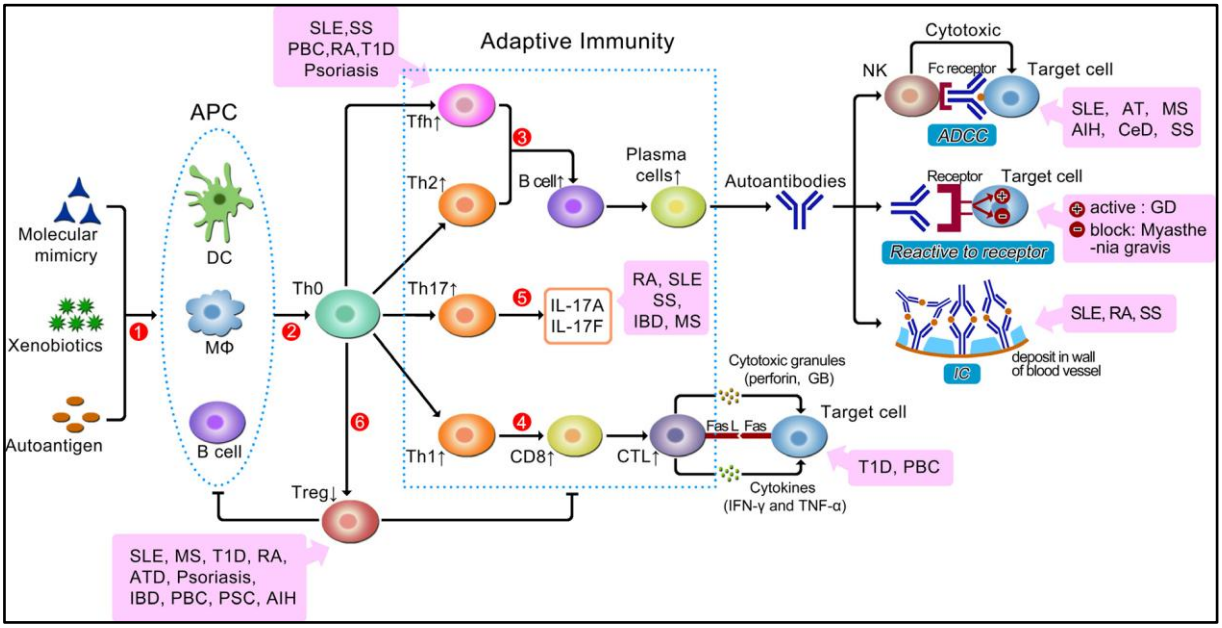


Figure 18: Autoimmunity is a result of a multi-orchestrated immune response[21]

Autoimmunity is a result of a multi-orchestrated immune response. (1) Through molecular mimicry, xenobiotics and antigens are recognized by antigen-presenting cells (APCs), which subsequently activate innate immune cells, that is dendritic cells (DCs), macrophages and natural killer cells (NKs). (2) T-cell immunogenic peptides are generated by APCs and are 'presented' to uncommitted T helper (Th0) lymphocytes, which then differentiate into Th2, T follicular helper (Tfh), Th17, Th1 and T regulatory cells (Tregs). (3) Th2 and Tfh cells facilitate B-cell activation, maturation and differentiation into plasma cells and ultimately autoantibody production. Through different mechanisms, autoantibodies may mediate tissue damage. (4) Th1 cells stimulate development of cytotoxic T lymphocytes. By secretion of

cytotoxic granules, activation of Fas–Fas ligand or release of cytokines, autoreactive cytotoxic T lymphocytes (CTLs) cause tissue injury. (5) Increased Th17 has also been reported to correlate with the progression of autoimmunity. (6) Decreased Tregs, which negatively regulate innate and adaptive immunity, facilitate loss of tolerance in several autoimmune diseases, including systemic lupus erythematosus (SLE), multiple sclerosis (MS), type 1 diabetes (T1D), rheumatoid arthritis (RA), autoimmune thyroid disease (AITD), psoriasis, inflammatory bowel disease (IBD), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH).

6. Classification of autoimmune diseases:

Autoimmune diseases are classified into two categories :systemic (as in the case of systemic lupus erythematosus) or organ-specific (as in the case of type 1 diabetes mellitus)(Table1).

In systemic Autoimmune diseases tolerance is lost for self antigens expressed by many tissues. However in organ specific Autoimmune diseases the self antigens tissue restricted for a specific organ.

As mentioned earlier systemic Autoimmune diseases affect multiple organ, however clinical observation have noticed a difference in diseases expression between patients . This difference can be explained by the presence of genetic polymorphism, involving other genetic determinates that participate and shapes diseases expression [21 25].[21;25]

Some autoimmune diseases in humans

Disease	Self-antigen	Immune response
	ORGAN-SPECIFIC AUTOIMMUNE DISEASES	
Addison's disease	Adrenal cells	Auto-antibodies
Autoimmune hemolytic anemia	RBC membrane proteins	Auto-antibodies
Goodpasture's syndrome	Renal and lung basement membranes	Auto-antibodies
Graves' disease	Thyroid-stimulating hormone receptor	Auto-antibody (stimulating)
Hashimoto's thyroiditis	Thyroid proteins and cells	T_{DTH} cells, auto-antibodies
Idiopathic thrombocyopenia purpura	Platelet membrane proteins	Auto-antibodies
Insulin-dependent diabetes mellitus	Pancreatic beta cells	T_{DTH} cells, auto-antibodies
Myasthenia gravis	Acetylcholine receptors	Auto-antibody (blocking)
Myocardial infarction	Heart	Auto-antibodies
Pernicious anemia	Gastric parietal cells; intrinsic factor	Auto-antibody
Poststreptococcal glomerulonephritis	Kidney	Antigen-antibody complexes
Spontaneous infertility	Sperm	Auto-antibodies
	SYSTEMIC AUTOIMMUNE DISEASES	
Ankylosing sponkylitis	Vertebrae	Immune complexes
Multiple sclerosis	Brain or white matter	T_H1 cells and T_C cells, auto-antibodies
Rheumatoid arthritis	Connective tissue, IgG	Auto-antibodies, immune complexes
Scleroderma	Nuclei, heart, lungs, gastrointestinal tract, kidney	Auto-antibodies
Sjogren's syndrome	Salivary gland, liver, kidney, thyroid	Auto-antibodies
Systemic lupus erythematosus (SLE)	DNA, nuclear protein, RBC and platelet membranes	Auto-antibodies, immune complexes

Table 1 : human Autoimmune diseases classification[50]

IV. IMMUNOTHERAPY IN AUTOIMMUNE DISEASES:

Autoimmune disorders are related to a disturbed immune reaction against self antigens due to lost of self tolerance , leading to tissue destruction . these diseases evolve in three phases: initiation , propagation and resolution, where the perturbed functional balance between effector and suppressor immune mechanisms has been extensively investigated in the pathogenesis of the disorders.[34][34]

The major goals for treating autoimmune diseases are to induce improvement (remission or low disease activity), while arresting irreversible organ damage and minimizing treatment side effects. Although definitive cure and restoration of permanent immunological tolerance would be ideal, most treatments now do not achieve that goal.

Nowadays Treatments are often anti-inflammatory and/or immunosuppressive.

1. Treatment of autoimmune diseases: established therapy

Traditional therapies, based on glucocorticoids and non-specific immunosuppressive, chemotherapeutic agents, that form the foundation of current clinical practice for many years which aims to induce an immunosuppressive state, leading to a reduction of disease activity.

Those treatments are mainly palliative, without any specificity for the pathogenic mechanisms of the disease[33](Table 2). [12;33]

1.1 NON-SPECIFIC ANTI-INFLAMMATORY DRUGS (NSAIDs):

All major NSAID classes share the common mechanism of inhibiting cyclooxygenase. NSAIDs are used commonly in multisystem autoimmune diseases to treat constitutional symptoms, fever, arthritis, serositis, and headache. The potential adverse effects of NSAIDs often limit their use, particularly induction of gastritis (often with bleeding), reduced glomerular blood flow, hypertension, peripheral edema, and the association of high doses with increased risk for myocardial infarction. Therefore, for safety concerns, they are recommended most commonly for as-needed rather than continual use.[12]

Drug	Primary Mechanism of Action	Side Effects	Indications
Antimalarials	Inhibition of TLR-3/7, raising of lysozyme pH affecting antigen processing	Headache, pruritus, rash, neuropathy, corneal deposition, retinopathy	Systemic lupus erythematosus, rheumatoid arthritis, juvenile idiopathic arthritis, Sjögren's, juvenile dermatomyositis, palindromic rheumatism
Sulfasalazine	Inhibition of prostaglandin synthesis, inhibition of NFκB transcription, reduction of TNF, suppression of B cells	Elevated liver enzymes, leukopenia, agranulocytosis, megaloblastic anemia, GI or CNS side effects	Inflammatory bowel disease (ulcerative colitis), mild rheumatoid arthritis, psoriatic juvenile idiopathic arthritis
Leflunomide	Inhibits dihydroorotate dehydrogenase, affecting *de novo* pyrimidine synthesis	Elevated liver enzymes, diarrhea, rash, hair loss, hypertension, interstitial pneumonitis, class X teratogen	Rheumatoid arthritis
Methotrexate	Inhibits dihydrofolate reductase, interfering with purine and pyrimidine metabolism and amino acid synthesis	Elevated liver enzymes, oral ulcers, diarrhea, mild hair loss, pneumonitis, infections, bone marrow suppression	Rheumatoid arthritis, psoriasis and psoriatic arthritis, seronegative spondyloarthropathies, arthritic manifestations of systemic lupus erythematosus, granulomatosis with polyangiitis, steroid sparing agent
Cyclophosphamide	Alkylating agent that inhibits cell division by cross-linking DNA and reducing DNA synthesis	Infections, bladder toxicity, secondary malignancy, premature ovarian failure, infertility, neutropenia	Systemic lupus erythematosus nephritis or other life-threatening manifestations, transverse myelitis, systemic sclerosis, granulomatosis with polyangiitis, polyarteritis nodosa, rheumatoid vasculitis
Mycophenolate mofetil	Inhibits inosine monophosphate dehydrogenase, affecting *de novo* purine synthesis in activated lymphocytes	Diarrhea, gastrointestinal upset, infection, bone marrow suppression, neoplasia, rash, tremor	Systemic lupus erythematosus nephritis, myasthenia gravis
Azathioprine	Purine antagonist and inhibits synthesis of DNA, RNA, proteins, cellular metabolism	Bone marrow suppression, infection, gastrointestinal upset, nausea, neoplasia	Maintenance therapy for systemic lupus erythematosus nephritis, ulcerative colitis, Crohn's disease, ANCA-positive vasculitis
Cyclosporine	Inhibits transcription of IL-2 production and proliferation of T lymphocytes	Renal toxicity, hypertension, neurologic side effects, skin or lymphoproliferative disorders, significant drug–drug interactions	Refractory ocular and mucocutaneous Behçet's disease, adult systemic lupus membranous nephritis, systemic sclerosis, severe ulcerative colitis, myasthenia gravis; typically not first-line therapy

Table 2: Established therapies for auto-immune diseases.[12]

1.2 Glucocorticoids:

Glucocorticoids (GC) have a broad range of anti-inflammatory and immunosuppressive effects on both the innate and adaptive immune system.

Effects of GC on immune cells include inhibition of signaling for T cell activation and IL-2 synthesis, down regulation of antigen-presenting cells via blockade of co-stimulatory molecules, immune deviation toward Th2 cytokines, and induction of T cell apoptosis . GC are often used to control acute manifestations of inflammatory and autoimmune disorders. [12]

2. Immunotherapy:

Immunotherapy is a treatment strategy based on modulating the immune response either by enhancing immunity (immune-stimulation) or decreasing immunity (immune-suppression) depending on the immune-pathological mechanism involved in the etiology of the disease.

Immunotherapy is a type of treatment that uses immunological tools, such as monoclonal antibodies, receptor-immunoglobulin fusion proteins, vaccines and immune cells[35].[35] Such therapeutic options have only been available in the past 10 to 15 years.

So far, non-antigen- specific approaches, such as the blocking of tumor-necrosis factor, are achieving some success but the same is not true for antigen-specific approaches. An ambitious goal is that of inducing or, in the case of established autoimmune diseases, restoring immune tolerance to target auto-antigens.[35]

The treatment of human autoimmune diseases often occurs years after the onset of the pathogenic process, and despite our increasing knowledge of the cellular and molecular processes involved in immunity, the most effective targets for immunotherapy in the chronic phase of the disease are not obvious.

Components of the pathological cascade that have received most attention are[12;35]:

- Factors involved in lymphocyte homing to target tissues;
- Enzymes that are critical for the penetration of blood vessels and the extracellular matrix by immune cells;
- Cytokines: that mediate pathology within the tissues;
- Various cell types that mediate the damage at the site of the disease, as well as these cells' antigen-specific adaptive receptors, including the T-cell receptor (TCR) and immunoglobulin; and other toxic mediators, such as complement components and nitric oxide.

2.1 Non-antigen-specific approaches:

2.1.1 Costimulatory blockade:

Activation of T cells requires two main signals (Figure 21). The first signal is antigen recognition through the T cell receptor (TCR), and the second signal is a co-stimulatory signal provided by the cell presenting the antigen [antigen presenting cell (APC)]. If the first signal is received without the second, T cells become sub optimally stimulated, resulting in a state of unresponsiveness or anergy. [12;35]

Blocking co-stimulatory pathways is an attractive potential treatment for autoimmune disease.

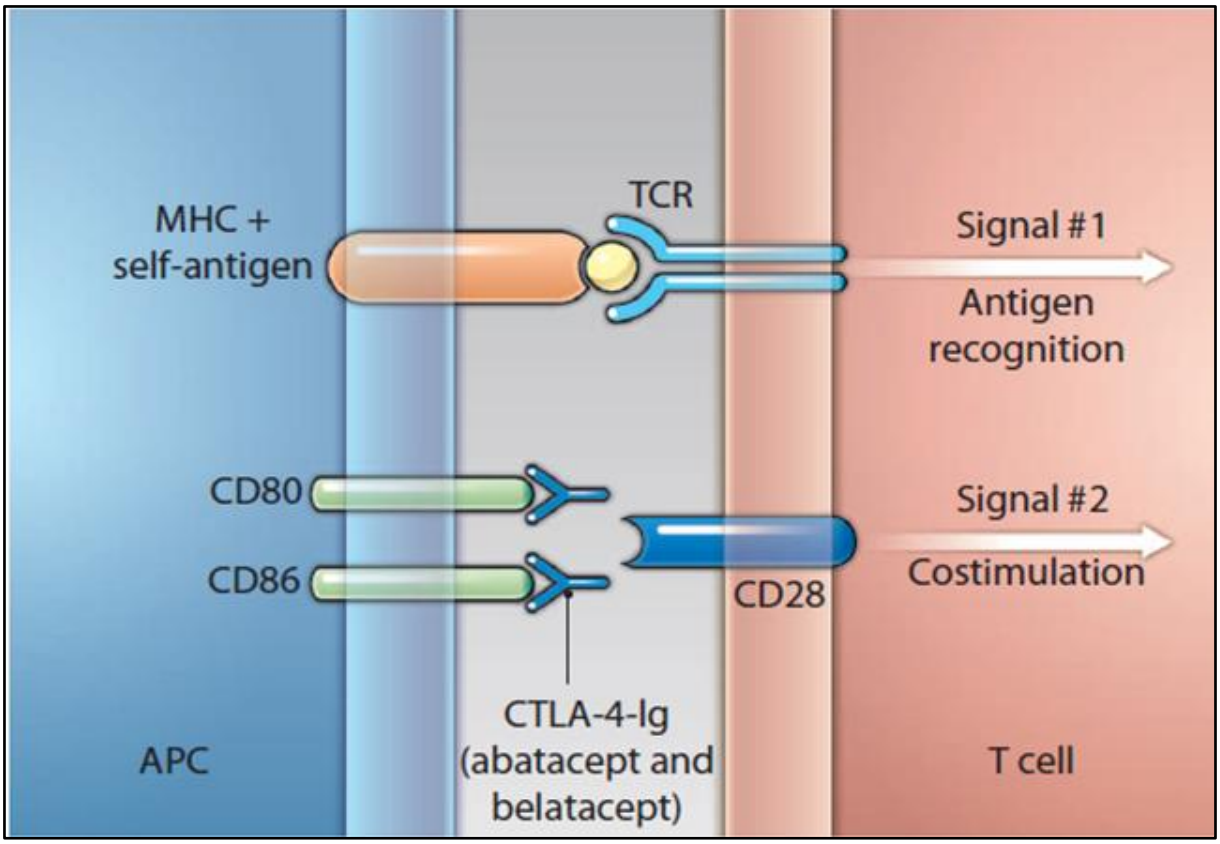


Figure 19: Costimulatory blockade as a method to treat autoimmunity.[12]

T cells require two signals to become fully activated. The first signal ("signal 1") is provided through the TCR upon recognition and binding of specific antigen presented in the context by MHC (major histocompatibility complex) molecules on APCs. The second signal ("signal 2") is a costimulatory signal provided by engagement of costimulatory ligands expressed on APCs with costimulatory receptors expressed on T cells. If T cells receive signal

1 without signal 2, they fail to be fully activated and are rendered functionally anergic. CD80 (B7-1) and CD86 (B7-2) binding to CD28 provides costimulatory signal to T cells.

The greatest success to date of this approach is cytotoxic T lymphocyte-associated antigen 4 (CTLA-4)-immunoglobulin (Ig), which directly prevents co-stimulation mediated by CD28 (Figure32).

Example : abatacept and belatacept approved for the treatment of rheumatoid arthritis , psoriasis.

2.2 Targeting T-cell antigens:

2.2.1 AntiCD3 :

Anti-CD3 antibodies were the first therapeutic antibodies introduced in clinical practice, initially used to treat and prevent renal allograft rejection due to a potent immunosuppressive action.

The production of a humanized Fc domain mutated anti-CD3 mAb allowed to minimize their side effects and to use them as potential therapeutic arm for autoimmune disease also in allograft rejection .

Anti-CD3 mAb was first used in autoimmune diseases , to treat patients with recent onset type 1 diabetes, the results were encouraging , as anti-CD3 mAb not only induced immunosuppression , but also induces disease remission by restoring self-tolerance.[12;35]

2.2.2 Anti-CD4:

CD4 another possible target for autoimmune therapy. Anti-CD4 mAb was developed however the results were below the expectations .

Despite preventing disease (such as arthritis and experimental autoimmune encephalomyelitis, EAE), to an impressive extent in animal models, anti-CD4-antibody therapy, with either lytic or non-lytic monoclonal antibodies, has not successfully treated human rheumatoid arthritis, psoriasis or multiple sclerosis. [34]

Alternatively, failure to prevent disease might have been caused by the anti- CD4 antibody also inhibiting regulatory T cells that express CD4.[12;35]

2.2.3 Anti- IL2 receptor (CD25) :

Monoclonal antibodies targeting the alpha chains of IL2 receptors , have proven their immunosuppressive capacities in experimental data .

Two humanized mAbs to CD25 were developed : basiliximab/Simulects ; and daclizumab/Zenapaxs.[12]

In autoimmunity, anti-CD25 mAb prevented onset of collagen induced arthritis , insulitis, and diabetes in NOD mice and lupus nephritis .

Moreover humanized anti-CD25 antibodies appear beneficial for treatment of some severe autoimmune diseases, uveitis in particular.

In addition, anti-CD25 mAb especially dalclizumab, was used in combination with IFN , where significant results were obtained, for maintenance therapy in patients with recurrent/ relapsing disease significantly reduced the number of new brain lesions or the progression of existing ones as assessed by magnetic resonance imaging (MRI) when compared to IFN-β monotherapy.[12;35]

Nevertheless , anti-CD25 mAb present no tolerance promoting activity , perhaps because CD25 is also expressed on a subset of T cells endowed with regulatory/suppressor capacities that are critical in maintaining immune tolerance.

2.3 B cells antigens:

Given the ubiquity of auto-antibodies in autoimmune diseases, it was assumed that the antibody-producing cells, plasma cells, would be a good target for therapy and the CD20, a specific B cell antigen, is the appropriate target . Therefore, anti-CD20 antibody (RITUXIMAB) was developed and used to treat autoimmune diseases such as systemic lupus erythematosus, and rheumatic arthritis.

The effectiveness of anti-CD20 antibody was rather disappointing , in the mentioned diseases above, compared to the very encouraging results observed in multiple sclerosis or type 1 diabetes, two conditions where pathogenic T cells and not auto-antibodies are regarded as the main actors . This could be explained by the role of B cells as auto-antigen presenting cells.

Unfortunately, the effect was not long-lasting as immune tolerance was not induced.

Other anti-B cells antibodies were developed Ocrelizumab(anti-CD20) and Epratuzumab (anti-CD22) and were tested with an efficient effect on the target.

In addition, major hope is focused on antibodies blocking factors that sustain B cell differentiation and/or activation such as Belimumab an anti-BLyS/BAFF mAb, which is approved to treat systemic lupus erythematosus .

In combination with standard therapies Belimumab showed good effect and good safety profile.

New molecules that achieve B cell depletion/blockade have been recently introduced and include inhibitors of survival factors. Among them, Atacicept is a recombinant molecule (formerly referred to as TACI-Ig) coupling a human Fc fragment and soluble TACI the receptor for BlyS/BAFF (B lymphocyte stimulator) and APRIL (a proliferation-inducing ligand).[12;35]

2.4 Adhesion Molecules:

The VLA-4 Integrins are adhesion molecules of fundamental importance to the recruitment of leukocytes in inflammation. The interaction between VLA-4 at the surface of activated lymphocytes and monocytes with its ligand VCAM-1 is essential for cell migration into inflamed parenchyma.

A specific humanized monoclonal antibody (Natalizumab) ,blocking of VLA-4, was used of in randomized placebo-controlled trial, in multiple sclerosis, and in Crohn disease.

Unfortunately reports indicated that chronic administration of this antibody gave rise to the risk of opportunistic brain infection caused by the JC virus (John Cunningham virus)[35].[35]

In addition, a humanized mAb, specific for the CD11a subunit of LFA-1(Leukocyte Function-associated Antigen (LFA)-1) ,Efalizumab , has been tested in psoriasis. When administered subcutaneously once a week, improvement was observed within 2 to 4 weeks, and lasted for up to 2 years.

Based on these results Efalizumab was approved in 2003 by the FDA for this indication. However, in 2009, it was withdrawn from the European and North American market due to three cases of PML(progressive multifocal leukoencephalopathy).[12]

2.5 Cytokines:

2.5.1 Blocking TNF Pathways:

Humanized mAbs to TNF proved a major breakthrough in the treatment of rheumatoid arthritis, The first chimeric neutralizing antibody to TNF is cA2 [human IgG1 named Infliximab

.

NGiven these results with Infliximab, other biologic agents against TNF were developed. Another chimeric anti-TNF mAb named CDP571 was clinically effective, as were two fusion proteins linking the TNF receptor molecules p55 or p75 to a human IgG constant region, Lenercept and Etanercept , respectively.

Moreover, mAbs to TNF were successfully used in severe Crohn's disease and have been approved for this use. Interestingly, at variance with what is observed in RA, TNF receptor fusion proteins were not effective in Crohn's disease.

Mechanism of action:	➢ Reduction in pro-inflammatory cytokine cascade, including reduction of ➢ IL-6, IL-1, GM-CSF and vascular endothelial growth factor (VEGF). ➢ Reduction in leukocyte trafficking owing to decreased

	expression of ➢ adhesion molecules and chemokines. ➢ Reduction in tissue-destructive enzymes, such as matrix ➢ metalloproteinases (MMPs), but levels of tissue inhibitor of MMPs are ➢ maintained. ➢ Reduction in angiogenesis through reduced VEGF production. ➢ Normalization of abnormal haematology: haemoglobin restored, platelets and fibrinogen reduced.
Clinical benefits:	➢ Reduction of symptoms including pain, stiffness and lethargy. ➢ Reduction in signs of active disease including tenderness and joint ➢ swelling. ➢ Reduction in cartilage and bone damage. ➢ Induction of tissue repair.
Potential side effects:	➢ Increased risk of infection due to reduced cytokine, for example increased risk of Tuberculosis and pneumonia. ➢ Increased levels of antibodies to double-stranded DNA; rare cases of ➢ drug-induced lupus can occur. ➢ Increased risk of lymphomas (not proven).
Differences between TNF-blocking drugs:	➢ Etanercept blocks TNF and lymphotoxin a (LTa). ➢ Infliximab and adalumimab, but not etanercept, are active in Crohn's disease. ➢ Difference most likely to be due to different dosing regimes. ➢ Alleged differences in cytotoxicity/apoptosis are controversial.

Table 3: Summary of the ANTI-TNF therapy in rheumatoid arthritis[34]

2.5.2 Antibodies to Interferon (IFN)-γ :

The central effects of IFN-γ in Th1-mediated immune responses include macrophage activation and up regulation of major histo-compatibility complex molecules[36].[36]

Anti-IFN-γ antibody were tested for treating RA and Crohn's disease , with promising results . Fontolizumab, a human anti-IFN-γ antibody, was tested for the treatment of Crohn's disease.[12]

2.5.3 Antibodies to Interleukin (IL)-12 (p40) :

Interleukin (IL)-12 promotes the differentiation of helper Th1 lymphocytes that are IFN-γ and IL-2 producers.[36]

The importance of the IL-12/IFN-γ and IL-23/IL-17 pathways in the pathophysiology of psoriasis, multiple sclerosis, and Crohn's disease fostered the development of antibodies directed to the p40 (shared between IL12 and IL 23) subunit which could therefore inhibit both IL-12 and IL-23.[35]

Ustekinumab, a human anti-p40 antibody, was shown successful in psoriasis, psoriatic arthritis, and Crohn's disease, but not in multiple sclerosis.[12]

Ustekinumab has proven great results as a therapeutic tool , in psoriasis with Long-term efficacy over 3 and even up to 5 years with a good safety profile. It showed, also a high rate remission in Crohn's moderate to severe disease resistant to TNF blockers.[12]

2.5.4 Antibodies to Interleukin (IL)-6:

IL-6 had been identified as the key growth factor for plasma cells and multiple myeloma B cells. The first IL-6 neutralizing antibodies were used mainly for inhibiting tumor growth (in lympho-proliferative diseases) . However, a major problem was that IL-6/anti-IL-6 complexes were not eliminated, which, in fact, prolonged the half-life of the cytokine . This difficulty was overcome by targeting the IL-6 receptor (IL-6R) by a humanized antibody (Tocilizumab).[12]

Tocilizumab was approved for refractory rheumatoid arthritis in 2010 and for systemic juvenile arthritis in 2011. The antibody is also used in Castleman's disease.

In rheumatoid arthritis, Tocilizumab induces rapid and sustained improvement including normalization of indices of inflammation (CRP), a reduction of radiological joint damage, and inhibition of B cell hyperactivity.[12]

2.2 Antigen-specific approaches:

The adaptive autoimmune response becomes more complex as disease progresses, owing to the generation of T-cell reactivity and antibodies to other local molecules — a concept known as epitope spreading.

Thus, in the chronic stage of the disease, the adaptive immune response targets several different molecules at the anatomical site of the disease.

Immunological tolerance to a wide spectrum of antigens (and auto-antigens) can be induced by parenteral, nasal, or oral delivery of a soluble antigen.[12;35]

The auto-antigen-induced tolerance, whether using proteins, peptides or altered peptide ligands, is facing a number of obstacles including, limitation of the treatment to early disease stages; loss of therapeutic effectiveness as disease progresses; a long lag time to achieve efficacy. This, may represent a problem in the case of acute autoimmune responses; risk of disease acceleration by triggering rather than down- regulating the autoimmune response; and sensitization with potential risks of anaphylaxis and/or production of neutralizing antibodies leading to serious problems [37].[37]

2.3 Bone marrow transplantation :

Autoimmune diseases include genetic components expressed in the lymphoid and macrophage lineages qualified as stem cell disorders.[1] Hence patients with serious autoimmune diseases can be considered for high-dose immunosuppression followed by hematopoietic stem cell transplantation (HSCT).This strategy was initially based on clinical observations in patients with malignancies and concurrent autoimmune diseases as well as

results of HSCT in experimental models . The latter showed that all types of HSCT, whether allogeneic, syngeneic, or autologous, may induce high remission rates provided adequate conditioning regimens are administered.[12]

2.4 Cell therapy and gene therapy :

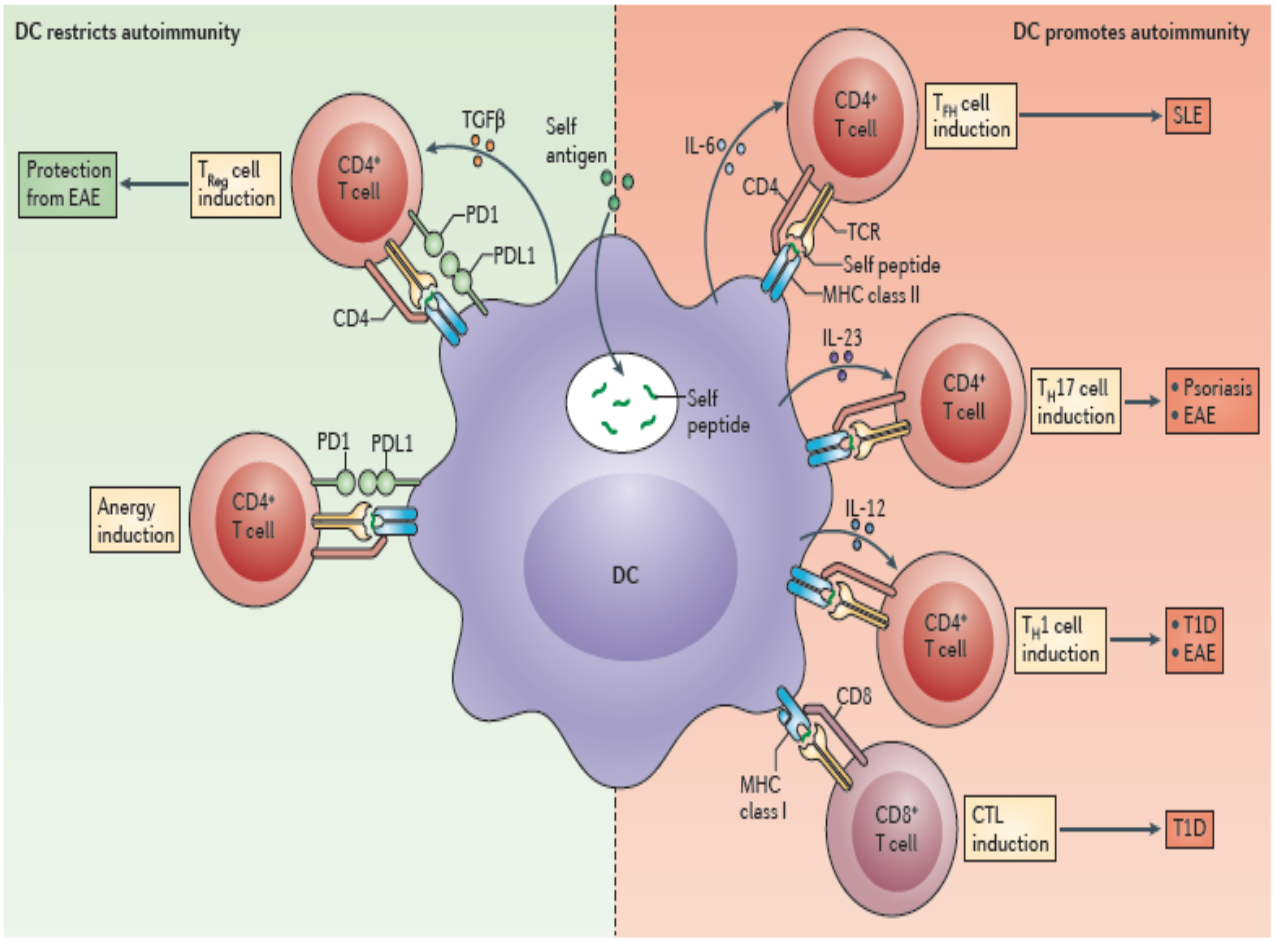
2.4.1 Cell Therapy:

The culture in vitro of specialized subsets of immune cells that can be re-administered into a subject with an autoimmune disease is another emerging therapy that has benefited from experience with cancer immunotherapy. Two cell types in particular have elicited interest, tolerogenic dendritic cells and regulatory T cells.[35]

Dendritic cells are normally potent stimulators of immune responses but, when appropriately manipulated in vitro, express powerful tolerogenic properties shown by suppression in vivo of alloimmune and autoimmune responses. Several factors influence this tolerogenic capacity of dendritic cells, including the precise subset of dendritic cell considered, and their degree of differentiation/maturation: immature or “semi-mature” dendritic cells are tolerogenic whereas mature dendritic cells are immunogenic. Several in vitro procedures have been described to derive tolerogenic dendritic cells, including treatment with CTLA-4Ig , IL-10 , vitamin D3 , or TGF-β[16].[16]

The cellular and molecular mechanisms that drive the modulatory capacity rely on a capacity to initiate states of peripheral tolerance: anergy, immune deviation, or induction of regulatory T cells.

The culture of regulatory T cells is another option. According to recent data, in vitro expanded CD25 regulatory T cells were highly effective in reversing established diabetes in NOD mice (Figure 20).[35]



| Potential roles of DCs in autoreactive T cell responses. Depending on the inflammatory context and the expression of cell-intrinsic regulators, dendritic cell (DC)-mediated presentation of self antigens might promote or inhibit autoimmune responses; for example, the presentation of self antigens to T cells in the context of the programmed cell death protein 1 (PD1)—PD1 ligand 1 (PDL1) interaction and/or transforming growth factor-β (TGFβ) signalling can lead to anergy in self-reactive T cells or it can promote their development into regulatory T (T_{Reg}) cells (left panel). By contrast, if DCs take up and present self antigens to T cells in the context of pro-inflammatory mediators (such as interleukin-6 (IL-6), IL-12 and IL-23), they can promote the development of self-reactive effector CD4+ T cells and cytotoxic T lymphocytes (CTLs). These self-reactive T cells might contribute to pathological autoimmune responses, such as experimental autoimmune encephalomyelitis (EAE) in mice, or systemic lupus erythematosus (SLE), psoriasis and type 1 diabetes (T1D) in patients. TCR, T cell receptor; T_{FH}, T follicular helper; T_H, T helper.

Figure 20: Roles of dendritic cell in autoreactive T cell response.[35]

2.4.2 Gene Therapy :

Gene therapy offers the potential to treat a wide range of inherited and acquired human diseases. In general, this approach involves the treatment of disease by introducing new genetic instructions into the tissues of patients in order to compensate for abnormal or missing genes or to convey a new function. Moreover, this involves the manipulation of gene expression in somatic cells that are corrective to the patient, but not inherited by subsequent generations. The therapeutic genes are transferred into the cells of the patient either through the use of recombinant virus vectors or plasmid DNA conjugates.[35]

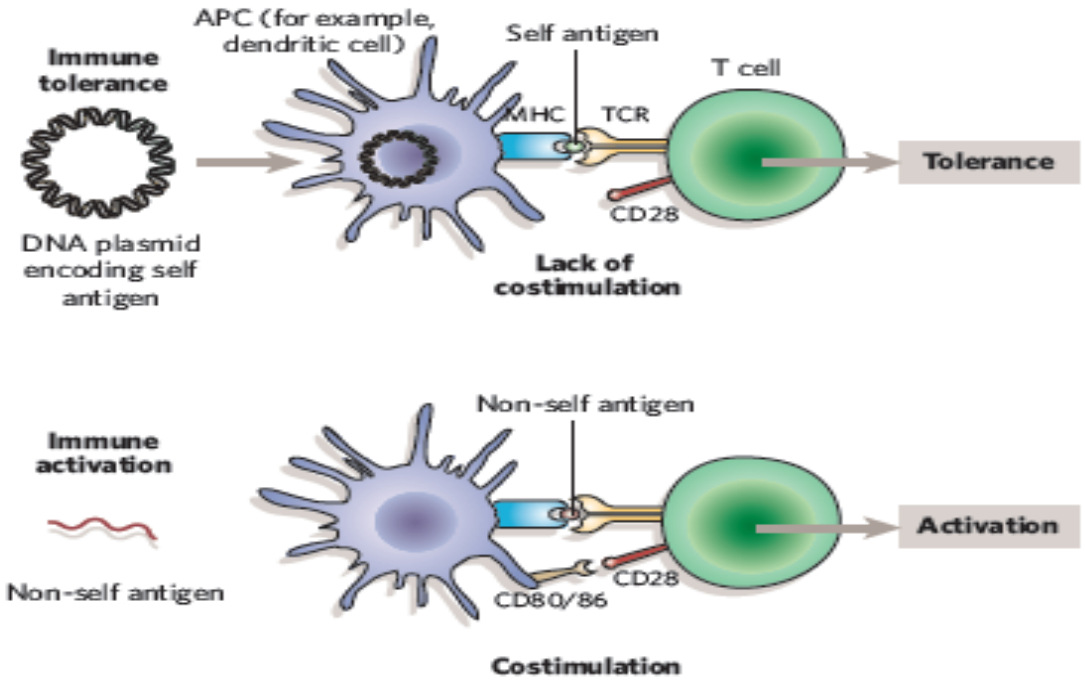
Targets of gene therapy in autoimmune diseases vary from correcting gene defects, Introduction of immune-modulating molecules to Interference with signaling processes involved in autoimmunity .[36]

Interference with signaling processes involved in autoimmunity

Whereas studying the effects of cytokines and cytokine inhibitors has been the main focus of gene therapy in auto- immunity research in the past, more and more studies are looking at alternatives for modulating autoimmune processes. Among these approaches are induction of apoptosis in pro-inflammatory cells, prevention of apoptosis in tissue cells, interference with TCR signaling, tolerance induction in immune effector cells, and various other strategies.

TCR signaling is another attractive target for gene therapy of autoimmune diseases. T-cell activation requires two signals.

The administration of a gene encoding a CTLA-4-Ig fusion protein is a successful strategy , that has proven its efficacy in animal trials .also the induction of T-cell tolerance is interesting as an antigen specific approach to induce tolerance, that is based in the use DNA constructs that are designed to promote the tolerization of immune responses. The figure bellow describe (Figure 21) the use of the technique in EAE (Experimental autoimmune encephalomyelitis).[16]



| Generating immune tolerance by using 'tolerizing' DNA vaccines. A DNA plasmid encoding a self antigen is transcribed and translated in a dendritic cell, but its expression does not stimulate the innate immune system enough to upregulate costimulatory molecules. A further reduction in costimulation is caused by the removal of CpG motifs in the plasmid. The presentation of self antigen by APCs without adequate costimulation leads to anergy or tolerance of T cells, because of the lack of interaction between CD28 with CD80 or CD86 (refs 72, 73). In contrast, conventional immunization, with a foreign antigen, leads to effective presentation of antigen in the MHC molecules with adequate costimulation, and leads to productive cytokine cascades and gene activation.

Figure 21:Immune tolerance by tolerizing DNA vaccines35.[35]

2.5 Plasmapheresis:

Plasmapheresis is based on plasma exchanges aiming to remove autoantibodies, immune complexes and other pathological metabolites involved in the physiopathology of several autoimmune diseases. In practice two main methods of plasmapheresis are used, centrifugal and filtration. The first method uses continuously-flowing or fractional

centrifugation. The second method is more physiologic. It is based on filtering the blood in special plasma filters. Using this immunotherapy, improvement was observed in several autoimmune diseases such as, bullous pemphigus and pemphigoid, Goodpasture's syndrome, glomerulonephritis with autoantibodies and myasthenia.[55]

2.6 Extracorporeal photochemotherapy:

Also known as photopheresis, extracorporeal photochemotherapy is a cellular therapy strategy based on a leukapheresis and subsequent ex vivo treatment using psoralen and ultraviolet A irradiation before reinfusion into the patient. This therapy aims to down regulates the immune response by inducing tolerance through the maturation of dendritic cells and the production of regulatory T cells. ECP is mainly used for treatment of Sezary syndrome, graft-versus-host disease, organ graft rejection and autoimmune diseases. However, the long-term effects and various treatment protocols require more investigation in order to extend to use of this therapy.[54]

V SYSTEMIC VASCULITIS :

1. Introduction :

Vasculitis is defined as inflammation of the blood vessels and can be aseptic or caused by invasion of the vascular wall by microorganisms.

The diverse clinical manifestations of noninfectious vasculitis are dependent on the location and size of the inflamed blood vessels and the immunopathogenesis of the lesions[38]. [38]

There are three major categories of systemic vasculitis : large vessel vasculitis (chronic granulomatous arteritis), medium vessel vasculitis (necrotizing arteritis), and small vessel vasculitis (necrotizing polyangiitis) (Figure 22). [12]

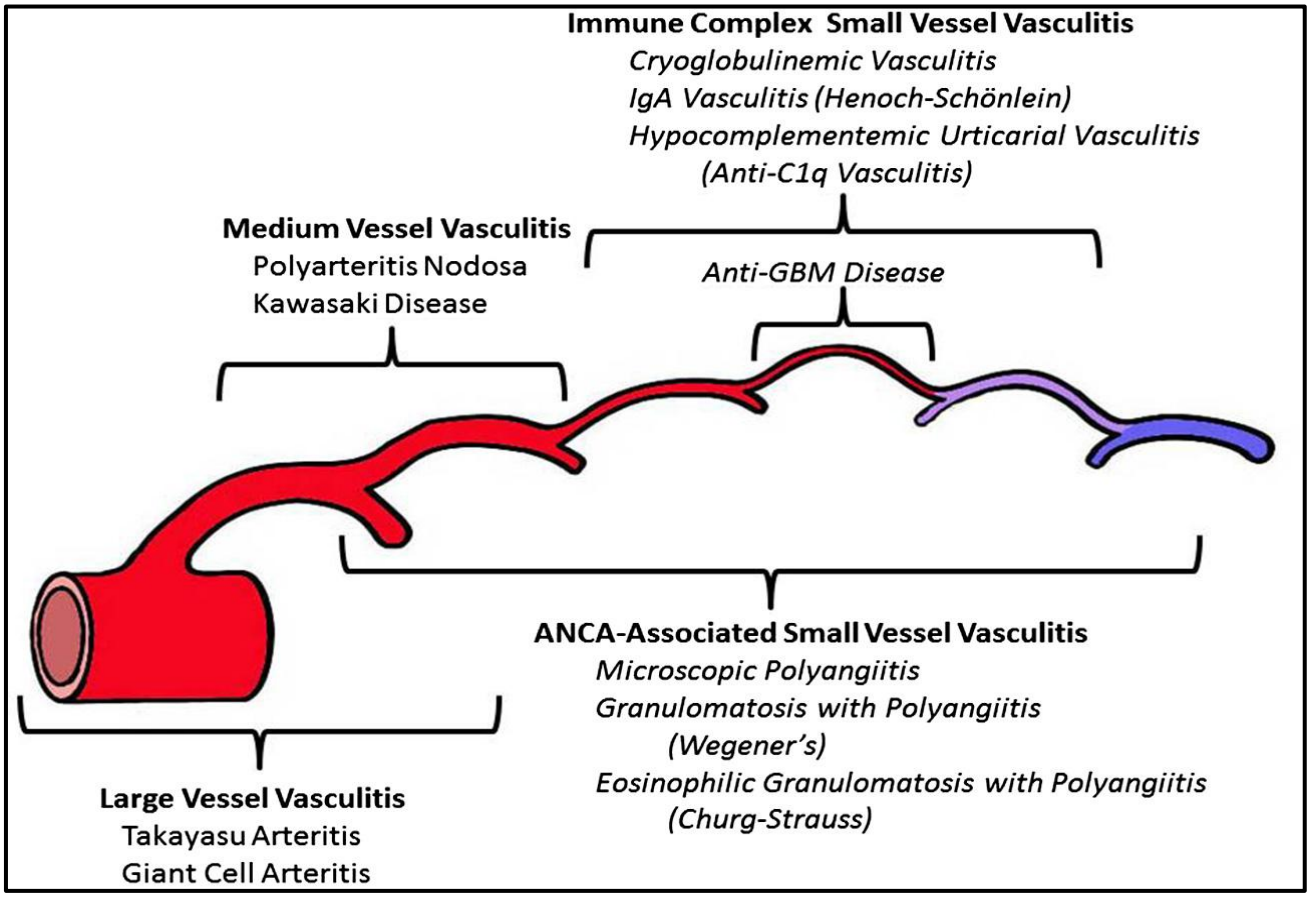


Figure 22: Overlapping predominant vascular distributions (brackets) of large vessel vasculitis, medium vessel vasculitis, and small vessel vasculitis.[12]

As such, vasculitis is a clinically heterogeneous group of disorders. clinical manifestations can vary widely and require different diagnostic and therapeutic approaches. [37]

Since most of our patients population are diagnosed with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), we will focus on medium and small vasculitis.

Antineutrophil cytoplasmic autoantibody (ANCA)- associated diseases are small-vessel vasculitides, encompassing granulomatosis with polyangiitis (GPA, formerly known as

Wegener's granulomatosis), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (formerly known as Churg-Strauss syndrome). These diseases are characterized by no or few immune complexes in the tissue and the presence of specific types of ANCAs, upon which the nomenclature of these diseases is now based (Table 4).

CHCC 2012 definitions of AAV[9]
GPA
Granulomatous inflammation usually involving the respiratory tract
Small-vessel necrotizing vasculitis
Necrotizing glomerulonephritis is common
MPA
Small-vessel necrotizing vasculitis
Necrotizing glomerulonephritis is very common
Pulmonary capillaritis often occurs
EGPA
Eosinophil-rich granulomatous inflammation of the respiratory tract
Small-vessel necrotizing vasculitis
Blood eosinophilia
Asthma

Abbreviations: AAV, anti-neutrophil cytoplasmic antibody-associated vasculitis; CHCC, Chapel Hill Consensus Conference; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis.

Table 4: Definition of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis [38]

ANCA asscociated vaculitis represent the only experimental model where antibody ctotoxicity against vessel membranes is well established (figure 16).

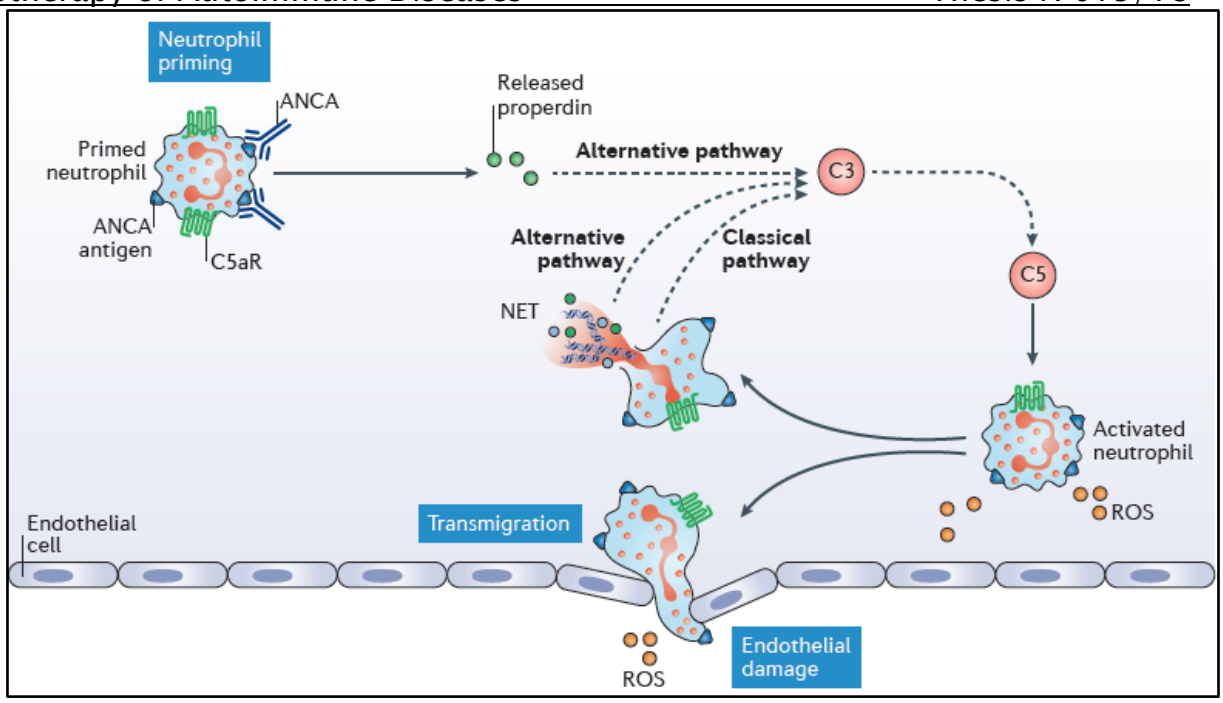


Figure 23: Schematic overview of complement activation in anti-neutrophil cytoplasmic antibody (ANCA)-associate vasculitis[33]

Eosinophilic granulomatosis with polyangiitis is characterized by differences in pathogenetic mechanisms, genetic associations and a much lower frequency of kidney involvement and ANCA positivity than is observed in GPA and MPA.

2. Classification of vasculitis :

Because the etiologies of most forms of vasculitis remain unknown, the most valid basis for classifying vasculitis is the size of the predominant blood vessels involved. Under such classification schemes, vasculitis are categorized initially by whether the vessels affected are large , medium or small.[38]

Large generally denotes the aorta and its major branches (as well as the corresponding vessels in the venous circulation in some forms of vasculitis, e.g. Behcet's disease).

Medium refers to vessels that are smaller than the major aortic branches yet still large enough to contain four elements: an intima; a continuous internal elastic lamina; a muscular media; and an adventitia. In clinical terms, medium-vessel vasculitis is generally

macrovascular (vessels large enough to be observed in gross pathological specimens or visualized by angiography).

Small-vessel' vasculitis, which incorporates all vessels below the level of macroscopic disease, includes capillaries, post-capillary venules and arterioles.

The typical clinical manifestations associated with small-, medium- and large-vessel vasculitis are shown in Table 5.

Typical clinical manifestations of large-, medium- and small-vessel involvement by vasculitis.

Large	Medium	Small
• Limb claudication • Asymmetric blood pressures • Absence of pulses • Bruits • Aortic dilatation	• Cutaneous nodules • Ulcers • Livedo reticularis • Digital gangrene • Mononeuritis multiplex • Microaneurysms	• Purpura • Vesiculobullous lesions • Urticaria • Glomerulonephritis • Alveolar hemorrhage • Cutaneous extravascular necrotizing granulomas • Splinter hemorrhages • Scleritis/episcleritis/uveitis
Constitutional symptoms: fever, weight loss, malaise, arthralgias/arthritis (common to vasculitides of all vessel sizes).		

Table 5: The typical clinical manifestations associated with vasculitides39[39]

3. Disease activity :

An adequate tool for assessing disease activity in patients with AAV is the Birmingham Vasculitis Activity Score (BVAS), which categorizes organ involvement and disease activity in each organ system. BVAS has been validated and used as an outcome parameter in many trials. For GPA, a more specific disease activity score (BVAS/WG) has been proposed and has proven sensitive to changes in disease activity in a large clinical trial.[39]

For childhood vasculitis, generally, a specific activity score has been developed and preliminarily validated. Classification, disease stage identification and assessment of disease activity are a basis for treatment.

4. Therapeutic considerations:

In anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) Treatment is biphasic and tailored according to disease stage and severity (Table 6 and figure 23). Induction of remission(3-6 months) for rapid control of disease activity and maintenance of remission(for at least 18 months). Maintenance therapy aims to prevent disease relapse using less-toxic agents than those required for induction of remission. However, relapses are frequent and require prolonged or repeated therapy. Moreover, current treatment strategies have substantial short-term and long-term adverse effects. [12;39]

The mortality of patients with ANCA-associated vasculitis (AAV) consequently remains increased compared with general population, owing to increased rates of infections, malignancies and cardiovascular events.[39]

Disease stages in ANCA-associated vasculitis

Disease stage	EUVAS and EULAR definition[53,61]	Systemic vasculitis outside ENT or lung	Threatened vital organ function	Serum creatinine (μmol/l)
Localized	Upper and/or lower respiratory tract disease without further systemic involvement or constitutional symptoms	No	No	<120
Early systemic	Any disease without organ-threatening or life-threatening involvement	Yes	No	<120
Generalized	Renal or other organ-threatening disease	Yes	Yes	<500
Severe	Renal or other vital organ failure	Yes	Organ failure	>500
Refractory	Progressive disease unresponsive to standard therapy	Yes	Yes	Any

Table 6: Disease stages in AAV.[39]

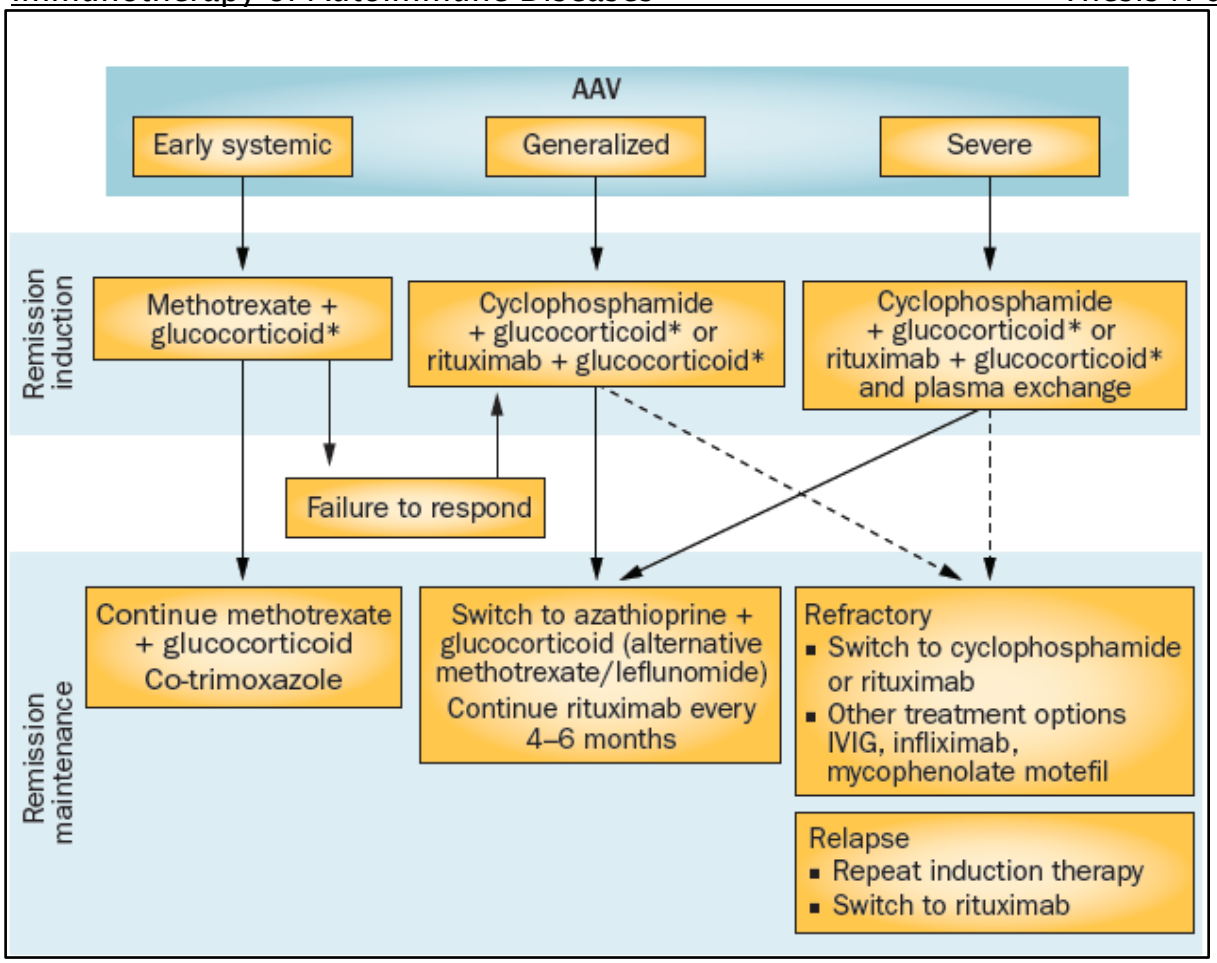


Figure 24: Treatment strategies for remission induction and maintenance of AAV.[40]

4.1 Refractory vasculitis :

Refractory AAV has been defined by the EUVAS and EULAR consensus study group (Box 1). According to the EUVAS/EULAR definition, the frequency of refractory AAV among participants in randomized controlled trials (CYCLOPS, MEPEX, NORAM, RITUXVAS, RAVE) is low, affecting only 4–5% of patients.

Current data from case reports suggest a response rate of 85% for Rituximab in patients with refractory AAV (complete remission ~60%, partial response ~25%) [40]. Rituximab can, therefore, be considered as an effective and well-tolerated second-line therapy for this group of patients, and might be the first choice after the failure of Cyclophosphamide treatment. One study suggests that response rates for vasculitis manifestations were excellent (complete remission or improvement in 90.6% of patients), whereas granulomatous manifestations (especially orbital masses) showed a high rate of failure to respond to Rituximab (unchanged

activity or refractory disease in 41.8% of patients) or might even progress despite this treatment.[49] In patients who do not respond to first-line use of rituximab, the addition of plasma exchange (especially for rapidly progressive glomerulonephritis and/or alveolar haemorrhage), or alternatively, switching to cyclophosphamide, may be considered. However, the risk of infection must be monitored even more thoroughly with such a combined treatment.[39]

- Unchanged or increased disease activity in acute stage after 4 weeks of treatment with standard therapy (daily oral cyclophosphamide, 2–3 mg/kg, or intermittent high-dose intravenous pulse cyclophosphamide 15 mg/kg and glucocorticoids)
- No response (defined as <50% reduction in disease activity score* and lack of improvement in at least one major item on the disease activity score list) after 4–6 weeks of treatment
- Chronic, persistent disease with presence of at least one major or three minor items on the disease activity score* list despite 8 weeks (>12 weeks) of treatment
- Intolerance of, or contraindications to, cyclophosphamide and glucocorticoids

*Birmingham vasculitis activity score, or granulomatosis with polyangiitis (formerly Wegener's granulomatosis)-specific Birmingham vasculitis activity score. Abbreviations: AAV, ANCA-associated vasculitis; EULAR, European League Against Rheumatism; EUVAS, European Vasculitis Study Group.

BOX 1 : Refractory AAV as defined by EUVAS and EULAR[39]

4.2 Maintenance of remission:

Current treatment strategies are highly efficient at inducing remission, with response rates of up to 90% in patients with AAV. However, relapses are frequent if maintenance therapy is not used, although the rate of relapse and time to first relapse varies considerably. Consensus guidelines suggest continuation of maintaining immunosuppression for at least 18–24 months (Table 7). After induction of remission, the use of a less-potent

immunosuppressive regimen to prevent relapses and damage related to disease activity must be balanced against the toxicity of the treatment.[39]

Recommendations for maintenance of remission of AAV according to EUVAS disease stage

Disease stage	Treatment	Dose	Trial
Localized	Co-trimoxazole	960 mg twice daily	NA
Early systemic	Methotrexate	20–25 mg per week and low-dose glucocorticoids	NORAM[18] WEGENT[64] LEM[92]
Early systemic with severe upper respiratory tract involvement	Co-trimoxazole	960 mg twice daily or three times per week	Stegeman *et al.*[78] Zycinska *et al.*[79]
Generalized	Azathioprine	2 mg/kg daily for 12 months, thereafter 1.5 mg/kg daily and low-dose glucocorticoids	CYCAZAREM[63]
Generalized	Methotrexate	20–25 mg per week and low-dose glucocorticoids	WEGENT[64]
Generalized	Leflunomide	20 mg daily and low-dose oral glucocorticoids	LEM[92]
Generalized	Rituximab	375 mg/m² or 0.5 g or 1 g infusions every 4–6 months	Ongoing

Abbreviations: AAV, antineutrophil cytoplasmic antibody-associated vasculitis; EUVAS, European Vasculitis Study Group; NA, not available.

Table 7: EUVAS recommendations for maintenance therapy[39]

4.3 Relapse of vasculitis :

Relapse has been defined as the reoccurrence or new onset of disease attributable to active vasculitis.

In patients receiving maintenance treatment for at least 18 months, the majority of relapses occur during tapering of glucocorticoids and cytotoxic agents or after the discontinuation of maintenance medication.[39]

VI BEHCETS DISEASE:

Behçet's disease (BD) is a chronic, relapsing, and debilitating systemic vasculitis of unknown etiology with the clinical features of mucocutaneous lesions, ocular, vascular, articular, neurologic, gastrointestinal, urogenital, and pulmonary involvement. The disease is much more frequent along the ancient “Silk Route” extending from Eastern Asia to the Mediterranean basin, compared with Western countries. The disease usually starts around the third or fourth decade of life. Male sex and a younger age of onset are associated with more severe disease. Although the treatment has become much more effective in recent years, BD is

still associated with severe morbidity and considerable mortality. The main aim of the treatment should be the prevention of irreversible organ damage.

1. Diagnosis criteria :

As there are no specific diagnosis tests for BD, the diagnosis is made on the basis of the clinical picture, with typical features balanced by exclusion of other differential diagnoses. Various criteria have been proposed to allow classification of the disease, of which the two most generally used are the The International Study Group (ISG) and The International Criteria for Behçet's disease (ICBD) (Table 8)[41].[41]

Genital aphthosis	Two points
Ocular lesions	Two points
Oral aphthosis	One point
Skin lesions	One point
Vascular lesions	One point
Pathergy	One point
3 or more points satisfy criteria for BD	

Table 8 : The International Criteria for Behçet's disease[41][41]

2. Treatment of Behçet's disease :

Treatment of the disease has become much more effective in recent years because of advances in understanding the pathogenesis the underlying disease and availability of a wide spectrum of therapeutic agents. Although several effective treatments currently exist, none of them result in a total cure of the disease and some are associated with significant side effects. The choice of treatment is generally based on the clinical presentation and the site affected. However, the main aim of the treatment should be the prevention of irreversible organ damage, especially, during the early active phase of the disease[42].[39;42]

Recommendation
Any patient with BD and inflammatory eye disease affecting the posterior segment should be on a treatment regime that includes azathioprine and systemic corticosteroids.
If the patient has severe eye disease defined as >2 lines of drop in visual acuity on a 10/10 scale and/or retinal disease (retinal vasculitis or macular involvement), it is recommended that either ciclosporine A or infliximab be used in combination with azathioprine and corticosteroids; alternatively IFNα with c without corticosteroids could be used instead.
There is no firm evidence to guide the management of major vessel disease in BD. For the management of acute deep vein thrombosis in BD immunosuppressiv agents such as corticosteroids, azathioprine, cyclophosphamide or ciclosporine A are recommended. For the management of pulmonary and peripheral arteria aneurysms, cyclophosphamide and corticosteroids are recommended.
Similarly there are no controlled data on, or evidence of benefit from uncontrolled experience with anticoagulants, antiplatelet or antifibrinolytic agents in the management of deep vein thrombosis or for the use of anticoagulation for the arterial lesions of BD.
There is no evidence-based treatment that can be recommended for the management of gastrointestinal involvement of BD. Agents such as sulfasalazine, corticosteroids, azathioprine, TNFα antagonists and thalidomide should be tried first before surgery, except in emergencies.
In most patients with BD, arthritis can be managed with colchicine.
There are no controlled data to guide the management of CNS involvement in BD. For parenchymal involvement agents to be tried may include corticosteroids IFNα, azathioprine, cyclophosphamide, methotrexate and TNFα antagonists. For dural sinus thrombosis corticosteroids are recommended.
Ciclosporine A should not be used in BD patients with central nervous system involvement unless necessary for intraocular inflammation.
The decision to treat skin and mucosa involvement will depend on the perceived severity by the doctor and the patient. Mucocutaneous involvement should b treated according to the dominant or codominant lesions present.
Topical measures (ie, local corticosteroids) should be the first line of treatment for isolated oral and genital ulcers.
Acne-like lesions are usually of cosmetic concern only. Thus, topical measures as used in acne vulgaris are sufficient.
Colchicine should be preferred when the dominant lesion is erythaema nodosum.
Leg ulcers in BD might have different causes. Treatment should be planned accordingly.
Azathioprine, IFNα and TNFα antagonists may be considered in resistant cases.

central nervous system; IFN, interferon; TNF, tumour necrosis factor.

Table 9 : Nine recommendations on Behcet disease (BD) by EULAR .[52]

Drugs	Doses	Molecular/cell targets	Mechanism of action	Main indications	Main side effects/Toxicity
Interferon α	3 to 9. 10^6 units 3 times/wk	NK cells γδ T cells	↗ NK functions ↘ phagocytosis of neutrophils ↘ adhesion of T-cells ↘ free radical production	Uveitis	Influenza-like symptoms : fever, chills, headache, fatigue, arthralgias, depression, leucopenia
Thalidomide	100 mg/d	TNFα mRNA	↘ lymphocyte proliferation ↘ angiogenesis	Mucocutaneous	Teratogenicity, Neurotoxicity, Constipation
Anticytokines					
Anti-TNFα (infliximab) (etanercept) (adalimumab)	various doses	TNFα	Inhibition of cytokine signaling	Uveitis, Gastrointestinal Neurological Refractory BD	Respiratory infection Reactivation of tuberculosis
Anti-IL1 (gevokizumab)	0.3 mg/kg (single infusion)	IL-1β		Uveitis	
Anti-IL-6 (tocilizumab)	8 mg/kg (infusion every month)	Soluble and membrane-bound IL-6 receptor		Uveitis, CNS	
Lymphocyte-targeted therapies					
Anti-CD20 (rituximab)	1000 mg (day 0 and day 15)	B-cell	B-cell depletion	Ocular lesions	Infusion reaction Pneumonia, herpes zoster infection
Anti-CD52 (alemtuzumab)	134 mg (single infusion)	Lymphocytes Macrophages	T-cell depletion	Uveitis, CNS	Infusion reaction

Table 10 : Biotherapies in BD: indications and side effects. [42]

1st line	*Topical: Antimicrobial agents, Sucralfate, Corticosteroids, Pimecrolimus Systemic: Colchicine, Colchicine + Benzathine penicillin
2nd line	*Topical: Anti-inflammatory agents, Amlexanox Systemic: Corticosteroids, Dapsone, Azathioprine, Thalidomide
3rd line	*Topical: Anaesthetics, Silver nitrate Systemic: Zinc sulfate, Rebamipide, Pentoxifylline, Methotrexate, Cyclosporine-A, IFN-α, Anti-TNF-α

Table 11 : Summary of evidence-based algorithmic treatment for mucocutaneous Behçet's disease.[51]

* Since the effectiveness of topical treatment is generally limited to the application area, it should almost always be associated with systemic therapy.

1st line	*Topical: corticosteroids + mydriatics ± cycloplegic agents Systemic: Corticosteroids, Cyclosporine-A, Azathioprine
2nd line	IFN-α, Anti-TNF-α
3rd line	Methotrexate, Mycophenolate mofetil, Cyclophosphamide, Rituximab

Table 12 : Summary of evidence-based algorithmic treatment for ocular Behçet's disease.[51]

1st line	Colchicine, Colchicine + Benzathine penicillin, or anti-inflammatory analgesics
2nd line	Azathioprine, Corticosteroids
3rd line	Methotrexate, Salazopyrine, IFN-α, Anti-TNF-α

Table 13 : Summary of evidence-based algorithmic treatment for articular Behçet's disease.

[51]

1st line	Corticosteroids, Azathioprine, Cyclophosphamide,
2nd line	Anti-TNF-α
3rd line	Anticoagulation, Antiplatelets

Table 14 : Summary of evidence-based algorithmic treatment for Vasculo-Behçet disease.[51]

1st line	Corticosteroids
2nd line	Azathioprine, cyclophosphamide, Anti-TNF-α, IFN-α
3rd line	Methotrexate, Anticoagulation

Table 15 : Summary of evidence-based algorithmic therapy for Neuro-Behçet's disease.[51]

PATIENTS AND METHODS

I. OBJECTIVES:

The overall aim of this thesis is to verify whether immunotherapy is superior to the cytotoxic molecule in treating vasculitis.

II.PATIENTS AND METHODS

1. Study framework :

Data have been collected from both internal medicine department of the University hospital Hassan II in Fez.

This study is a retrospective, descriptive, comparative analysis involving cases who were diagnosis with vasculitis in the department.

2. Patients:

All patients diagnosed with vasculitis (primary or secondary) at the department of internal medicine at the university hospital Hassan II, Fez, from January 1st 2012 to march 31st 2017, (n= 117) were eligible.

Patients originating from other departments for treatment or evaluation.

3. Data Extraction:

A computer search of cases with vasculitis was achieved on the data collection system "HOSIX" using patient‘s identification. (ANNEX I)

4. Population studied:

4.1 Inclusion criteria:

All cases of vasculitis hospitalized in the department of Internal Medicine, responding to ACR criteria.

4.2 Exclusion criteria:

Patients diagnosed with vasculatis and whose files were lost or incomplete.

5. Statistical analysis:

All patients' data were coded and imported into MS Excel® worksheets and subsequently analyzed by epidemiology specialists using IBM SPSS Statistics in 3 steps.

STATISTICAL RESULTS

I. EPIDEMIOLOGICAL DATA:

1. Distribution by age :

We documented a mean age of 37,18 years ranging from 16 to 83, with a median of 34 years (SD: 13,038) (TABLE 16).

number	minimum	maximum	median	standard deviation
117	13	83	34	13,038

Table 16 : DISTRIBUTION OF PATIENTS BY AGE

2. Gender distribution:

We noticed a predominance of males over women in our study, 65 males that to say 55,6 % and 52 females that to say 44,4 % with a sex ratio of M/F= 1.26 (Figure 24) .

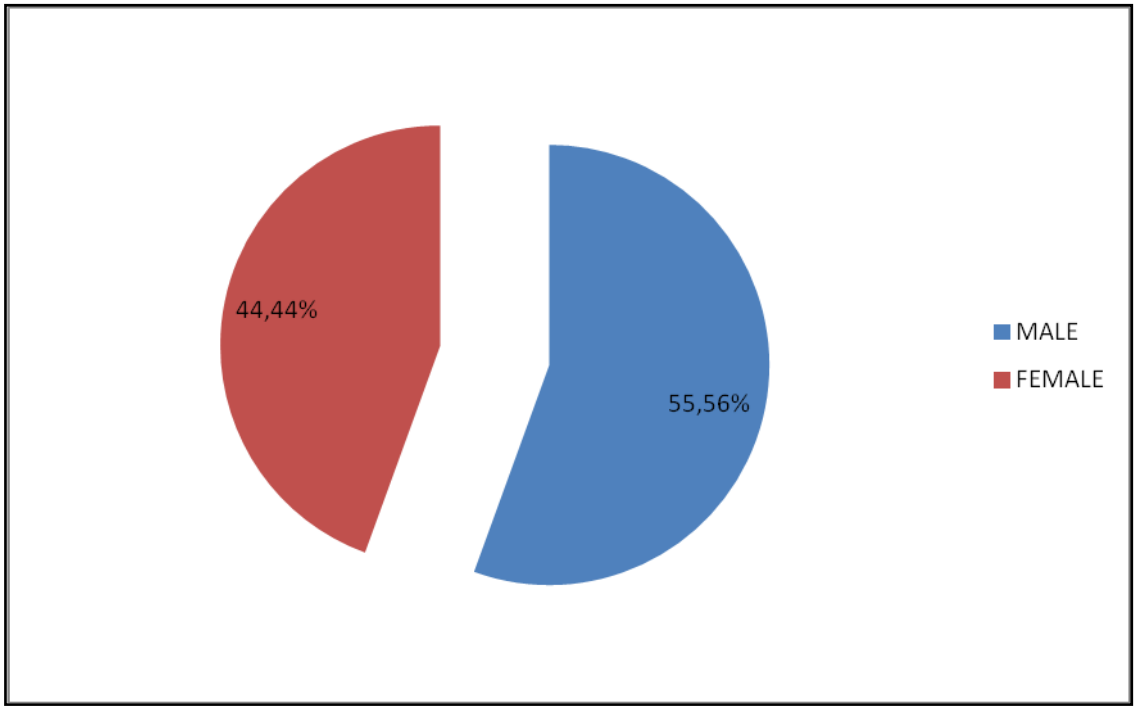


Figure 25 : Gender distribution

3. Distribution by area of origin:

Seventy six Cases, that to say 65 % , in our sample are from the area of Fez while only 41 patients were from other zones. Seven patients were from Meknes while the rest were from various regions (Figure 25).

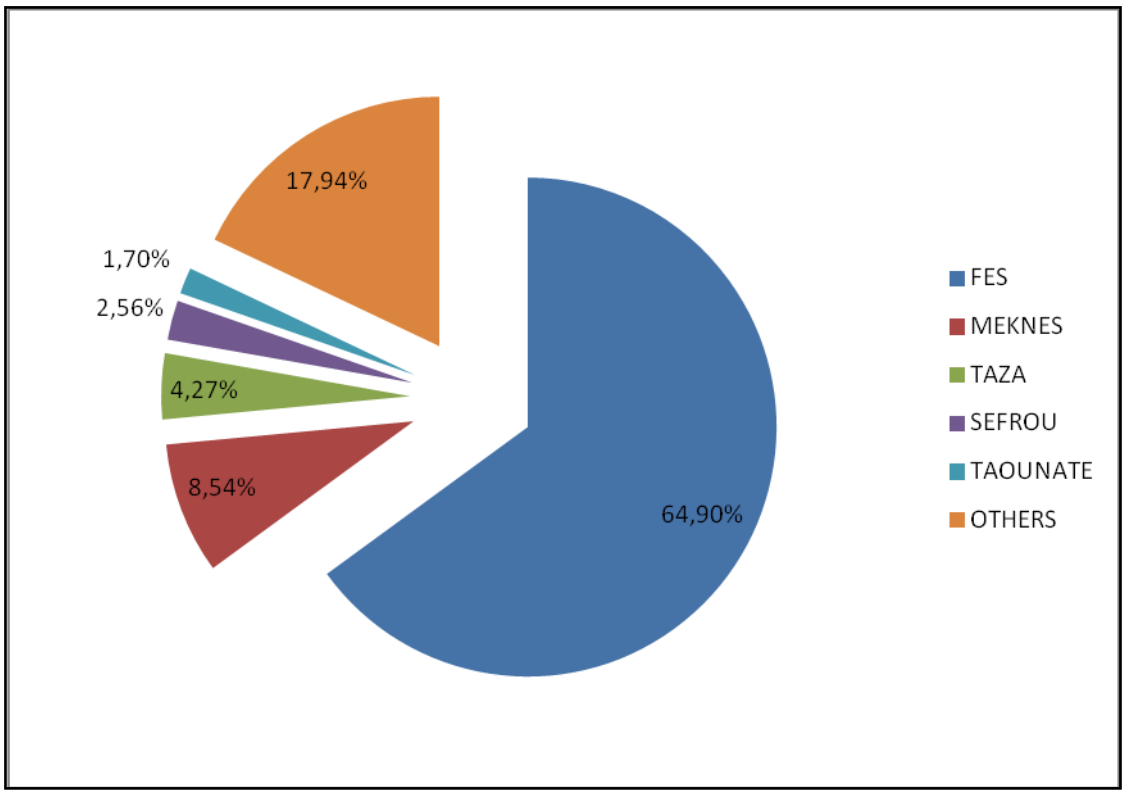


Figure 26: Patients distribution by area of origens

4. Health insurance:

We noticed that the major part of hospitalized and followed patients belong to the RAMED system, representing 62,4%.

II. CLINICAL STUDY:

1. Backgrounds :

1.1 Personal history:

Twenty of our patients, representing 17, 09 %, had a medical history as illustrated in the table below. High blood pressure, 8 patients (40%), is the dominant co-morbidities, followed

by diabetes and heart disease. we documented 2 patients with history of appendicectomy (Table17).

medical history	Patients(n=20)	Percentage
High blood pressure	8	40%
Diabetes	4	20%
Heart disease	4	20%
Tuberculosis	2	10%
Gastritis	1	5%
renal failure	1	5%

Table 17 : MEDICAL HISTORY

1.2 Toxic exposure:

Twenty one patients (17,94%) were smokers or had a history of smoking . While 9 patients (7,69%) had a history of alcohol consumption. Four patients were under depakine for their epilepsy.

1.3 Family history:

Three Patients had a history of vasculitis in their family.

2. Diagnosis:

The predominant vasculitis was behcet disease with 79 patients,that to say 67,5 %,where uveitis is the most representative with 89 % manifestation. It's followed by vasculitis secondary to lupus with 16,24% (n=19) , and Wegener with 6,8% (n=8).

PAN and takayasu were less found in our population sample with one case in each. two patients had secondary vasculitis , one of them had cryoglobulinemia (Figure 26).

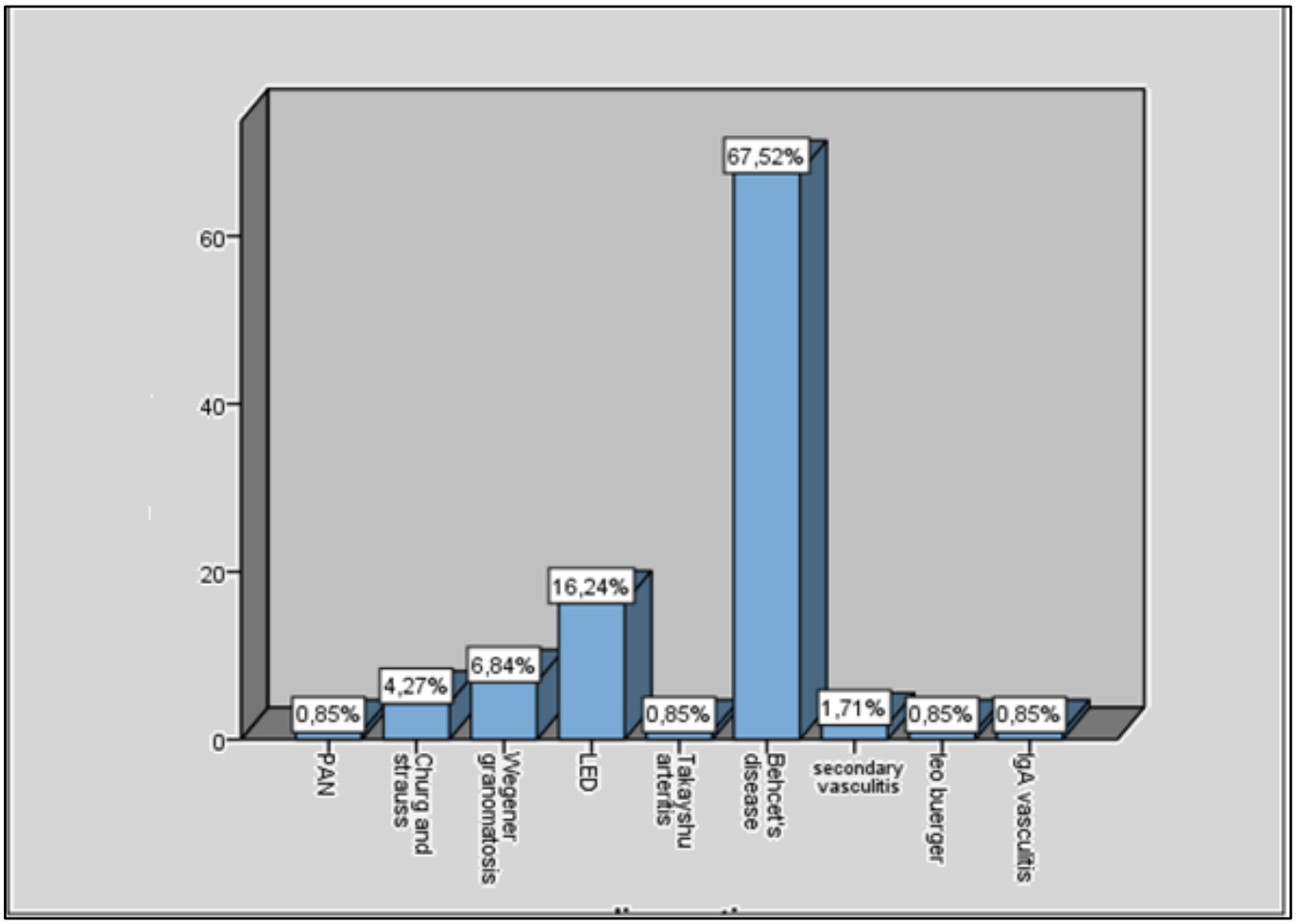


Figure 27 : patients distrubation by diagnosis

3. Para-clinical parameters:

3.1 Biology:

3.1.1 Cell Blood Count (CBC) :

Except for two patients, our populations had systematically CBC , the results of our population were as follows :

Leukocytosis was found in 16,2 % of patients (n=19) at the time of diagnosis , for 14,5 % of patients (n=17) had lymphopenia . Hypereosinophelia was reported in about 4,3 % of our patients .four patients were diagnosed with Churg and Strauss , while one patient had LED (Figure 27).

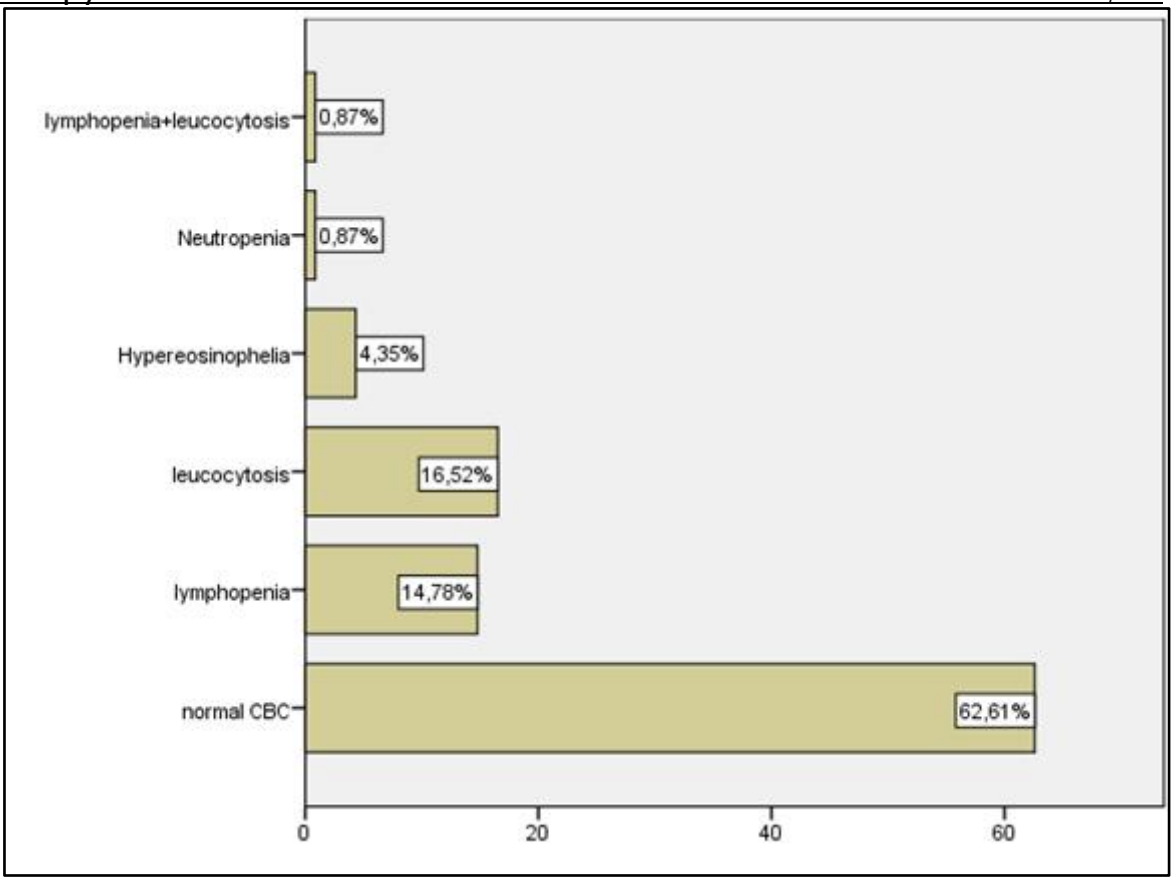


Figure 28: CBC anomalies in our population

3.1.2 Inflammation assessment:

A. Sedimentation Rate :

Accelerated Sedimentation Rate was found in 91 % in our study.The minimum was 17 while the maximum is 120 with a median of 60 (SD=31,6) (Table 18).

Number	minimum	maximum	Median	SD
117	17	121	60	31,6

Table 18: Sedimentation rate

B. CRP:

CRP value in our study varied from 0 to 300 with a median of 21. 79 % of our sample had elevated levels of CRP. While 26,6% (n=29) had a value higher than 20mg/ml .

3.1.3 Kidney assessment:

Renal testing results are as followed :

- Eleven patients out of 47 (23,4%) had an elevated serum creatinine , we defined elevated creatinine by level higher than 12 mg/dl. The minimum is 4 and maximum is 62 with a median of 8 (SD: 12,8)

- The maximum of blood urea nitrogen (BUN) is 1,8 and the minimum is 0,14 with a median of 0,36 (SD=0,37). The definition of elevated BUN is a level higher than 0,4 . in our population 16 patients out of 36had elevated BUN (44,4%) of the 39 patients who had PROTENURIA 24H ,proteinuria was higher than 500mg/24h in 20 patients (51 %). The minimum found was 0,025g/24h while the maximum was 27g/24h for the patients diagnosis with IgA vascilutis .

- Renal biopsy was performed in 4 patients , where the main indication was elevated level of proteinuria as the renal biopsy is not systematically performed . 3 patients had abnormal results while one patient Renal biopsy showed no anomaly.

3.1.4 pre-therapeutic assessment:

The pre-therapeutic assessment include many biological exams , of which serology BK crachat and liver enzyme:

- 3patients had positive HBS antigen , one patients was diagnosis with PAN while 2 patients had behcet disease

- Hepatit C serology was positive in 2 cases , both were diagnosis with churg and straus vasculitis

- NO positive HIV case was reported among patients of our sample

- Liver enzymes : 99 % of our patients had a normal serum enzyme levels

- ANCA serology were carry out for 18 patients , 14 were negatives, while 4(22,2%) patients had positive ANCA serology of which :

- One patient : c ANCA for patients diagnosis with churg and strauss
- Three patients : p ANCA , one had behcet, and the others wegner

➢ AAN were positive in 12 cases in our sample , 11 patients were diagnosis with LED while one patients had TAKAYSU vasculitis.

3.2 imaging studies:

Imaging studies used in the workup of patients with EGPA include chest radiography and chest computed tomography (CT). Other imaging studies are indicated for the complications of the disease and specific organ-system involvement, including abdominal CT scanning for pancreatitis, coronary angiography for myocardial ischemia and infarction, and echocardiography for congestive heart failure (CHF).

➢ Chest radiography was abnormal in 12 % (n=14) the mean anomalies were Pleural effusions and Pulmonary opacities

➢ 32,5 % of patients(n=8) patients with echocardiography (n=40) were abnormal with pericadic effusion, and VG hypertrophy with valvulitis.

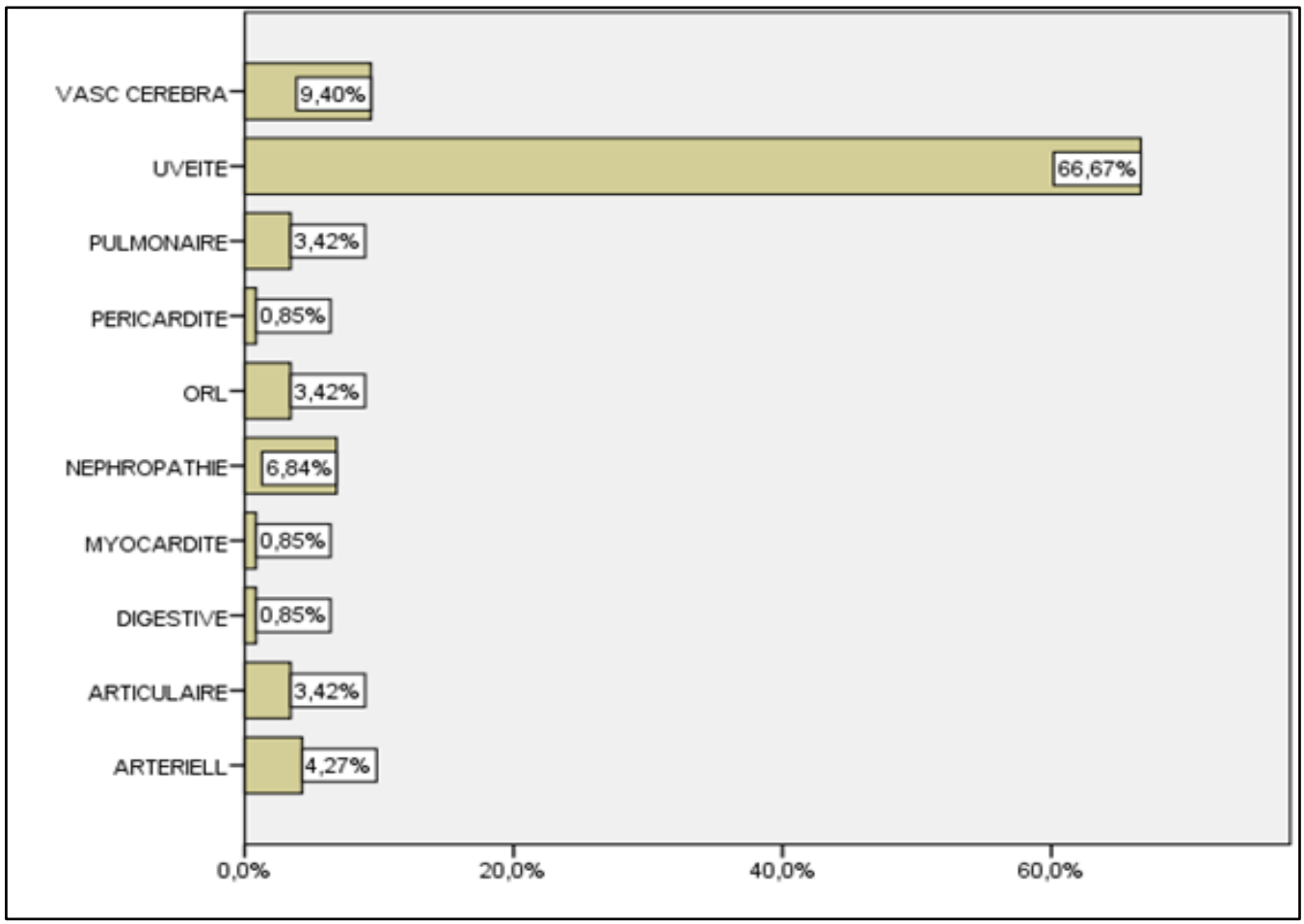
➢ 62 patients (52 %) had benefited from abdominal echography , 7 had an abnormal results , showing SMG , suscpiscion of pancreatitis .

➢ Abdominal CT was performed for 3 patients, 2 of them were diagnosis with pancretatitis.

➢ Cerebral CT has showed anomalies in 20 patients out of 26 patients that had cerebral CT: pachymeningitis and cerebral vein thrombosis, with ischemia for 1 patients that had ischemic stroke .

➢ Cerebral IRM has showed anomalies in 7 patients (6,9 %).

➢ Angio scanner was abnormal in 5 patients (4,9 %) objectiving veinal thrombosis .



4. Ophthalmic exam:

86,5% (n =84) patients had ocular involvement in their vasulitis . uveitis is the dominants ocular lesion ,with 94 %(n=79) .Most of patients had bilateral uveitis with 70 % (n=56) . Retinal vasculitis the most serious complication was reported in 37 patients (44,04%).

5. Treatment:

5.1 Indication :

In our study we registered a variety of clinical indication for therapy . The most representative indication was uveitis with 66,7% , and renal cause with 6,8 % . pericarditis was reported in only one patient. Cerebral vasculitis represent9,4 % of therapy indication , all patients had secondary vasculitis to SLE.

In our study 84 % of patients were hospitalized in internal medicine CHU Hassan 2 in order to receive their treatment (Figure 28).

Figure 29: indication for treatment by organ involvement

5.2 Molecules:

5.2.1 Corticosteroids :

78 % of patients in our simple received corticotherapy infusions of Methylprednisolone: 3 days bolus (15mg/kg/day) .While only 50 % were under oral corticotherapy .with a full dose of ,1mg/kg/day , with a median of 14 months.

5.2.2 cytotoxic drugs:

The cytotoxic drugs represent the first line of treatment of patients in our study to induce remission and maintenance.

5.2.2.1 Cyclophosamide :

It was used as first line molecule for 71,8 % of patients(n=84). with number of infusion that varies from 1 infusion to 18.

83 %of our treated patient received 6 infusions or more of cyclophosphamide, following the protocol : 0,6 g/m2 in day1, day15 and day 29, then 0,7 g/m2 every 21 days for 3 infusions.

In our study we evaluated patients evolution after 6 infusions(n=70) and results were as the following : 57 % response to cyclophosphamide with no relapse in the first 6 months . While 42,8 % patients(n=30) relapsed in the first 6 months.

5.2.2.2 Azathioprine:

61% of patients received azathioprine for maintenance therapy with a dose of 2,5mg//kg /day . with a median of 2 years of treatment.

Seven patients were lost,7died and 10 patients were maintained by immunotherapy .

5.2.2.3 Metothrexate:

Nine patients, that to say 7,7 % , in our study received metothrexate for their disease. The indications were as followed (Table 19) .

Indication	N. of patients
Wegener	1

takayashu	1
Behcet	3
LED	4

Table 19 : indication of Methotrexate by disease

5.2.3 Immunotherapy:

Immunotherapy is an new effective therapeutic molecules ,representing the perspective of the future.

In our population 30patients, that to say 25,6% , received immunotherapy . the main used molecules are Rituximab(n=15) and Infliximab (n=15).

Only 7 patients received immunotherapy for their non controlled disease by cytotoxic molecules .while the indication was predominantly the relapse of the vasculitis under cytotoxic molecules(Figure29).

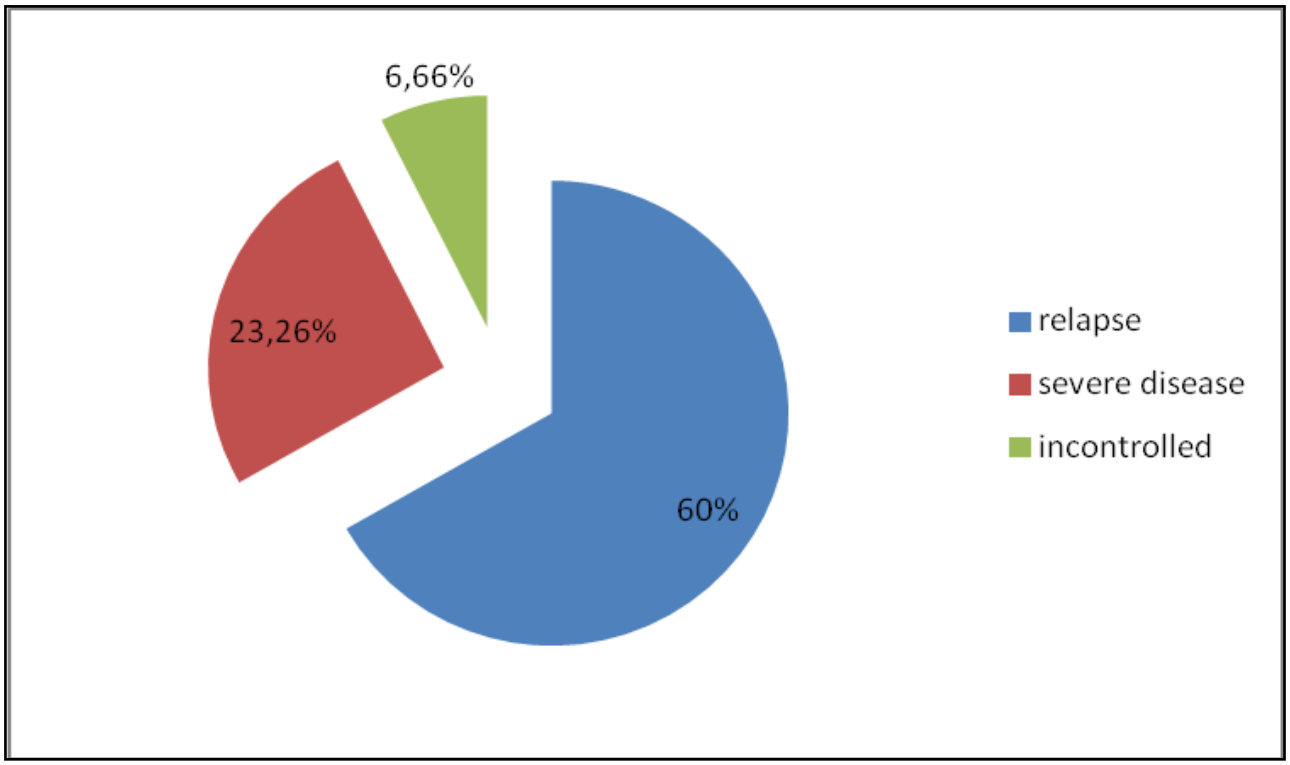


Figure 30: indication of Immunotherapy

5.2.3.1 RITUXIMAB:

Induction by Rituximab was given according to the vasculitis protocol : 375mg/m2 day1, day 7 et day14 and day 21.

Rituximab for maintenance was used for 8 patients with Rituximab 500mg every 3 to 6 months . while the rest of patients were maintain with Azathiopine.

5.2.3.2 Infliximab:

It is a Anti-TNF immunoglobulin indicated in many autoimmune diseases. The main indication in our sample was uveitis.

It was given according to the protocol: 3 mg/kg IV at 0, 2 and 6 weeks, then every 8 weeks. In 3 patients it was used in the first line, where the remaining patients it was indicated for relapse of the uveitis . The number of infusion vary from 4 as a minimum to 14 infusions With a median of 8 infusions.

5.2.3.3 PLASMAPHERESIS:

It was used for one patients diagnosed with PAN. The patient responded well to treatment , however he presented hypofibrinogenemia , a complication related to Plasmapheresis. Patients had received fibrinogen infusion before every sessions.

6. Evolution:

55% of patients responded to treatment. We registered 7 cases of death , while 7 patients were lost and no follow up was performed (figure30).

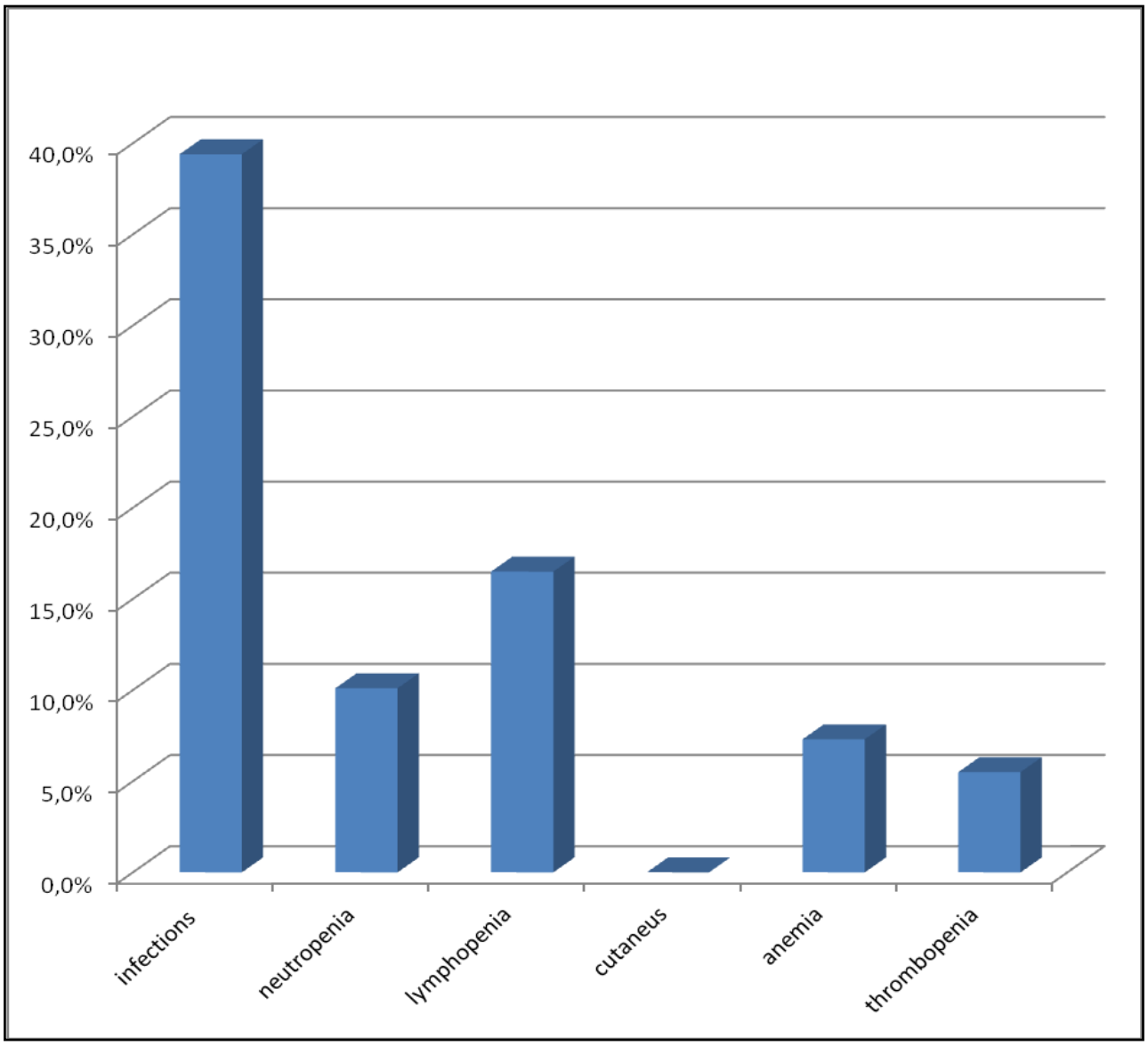


Figure 31: patients response to treatment.

7. Side effects:

In our sample, the most representative complication were infectious with 39,4% ; where fever and rhinopharyngitis are the most common and the mean cause of infusion's reports.

16,5% of patients had lymphopenia , while neutropenia was reported in 10% of the study's population mainly after receiving cytotoxic molecules (figure 31,32).

Figure 32: side effects of our patients

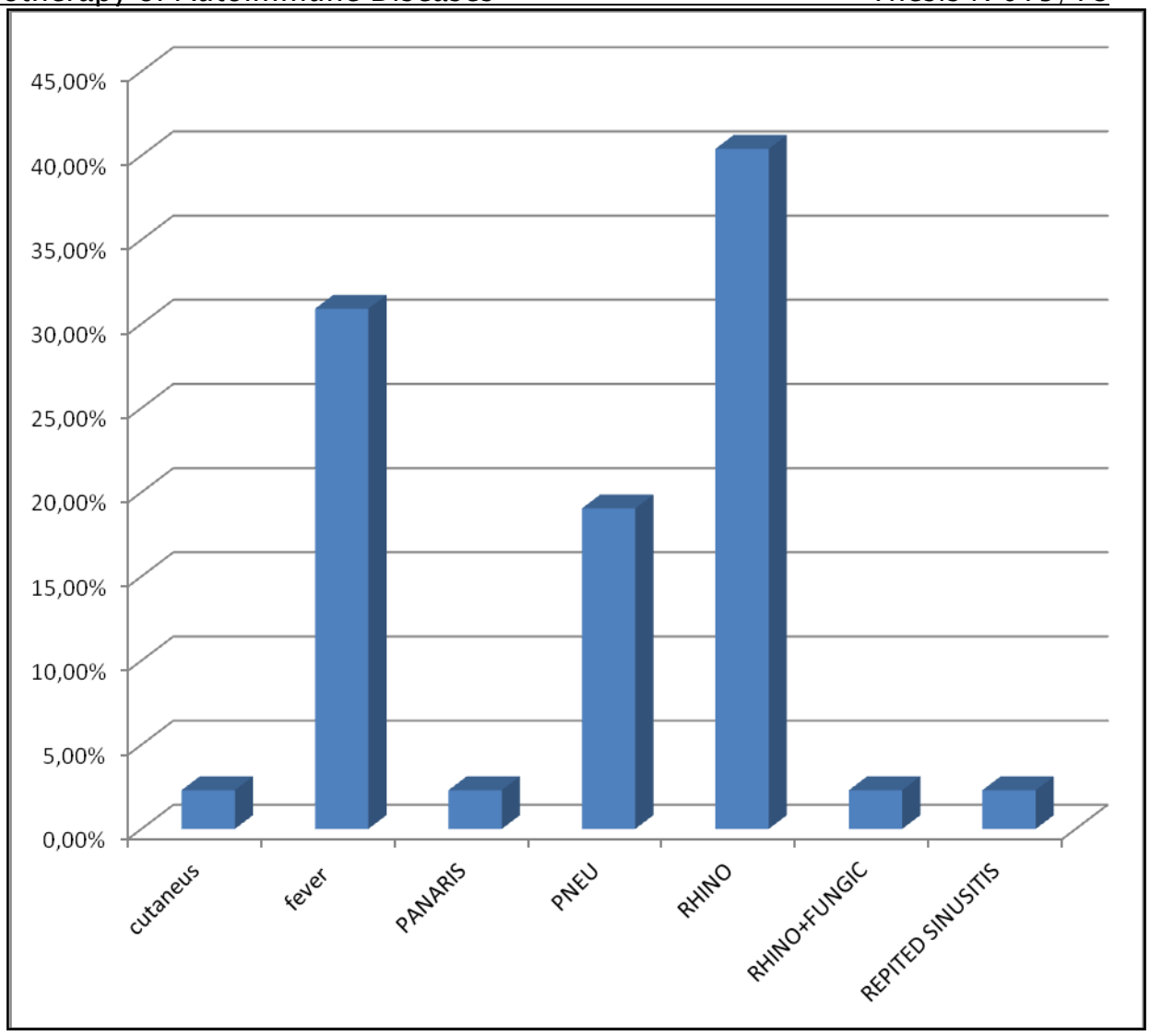


Figure 33 : distribution of infection by site

III. COMPARATIVE STUDY:

In these parte we will compare between the patients who had received immunotherapy and patients that were treated with immunosuppressive therapy, in terms of :

Baseline charrateristics: age and gender

Organ involvement

Evolution and response

Side effect and complications

1.Baseline characteristics :

The median age of patients who underwent immunotherapy 40 was higher than patients with immunosuppressive treatment 36(p=0,089).

In terms of gender, as shows the table bellow, we noticed that females were predominately treated with immunotherapy while the results showed that male represent 59,7 % of patients treated with cytotoxic molecules (p= 0,118) (Table 20).

	sexe	
	Female	**Male**
Patients under immunotherapy	17	13
Patients under cytotoxic molecules	35	52

Table 20 :comparative table of patients by age

2. Organs involvement:

There were no differences in regards of organ involvement between the two populations . Ocular lesion and renal lesions represent the major's organs targets of the diseases and the major indication for treatment(Table 21).

	Effective	Percentage
ARTERIELL	1	3,3
ARTICULAR	3	10,0
NEPHROPATY	4	13,3
PERICARDITIS	1	3,3
PULMONARY	3	10,0
UVEITIS	15	50,0
CEREBRAL VASCULIIS	3	10,0
TOTAL	30	100,0

Table 21 : distribution of patient receiving immunotherapy by organ involvement

all patients with pleura pulmonary lesion, were treated only with cytotoxic molecules in both case.

	Effective	Percentage
Churg and strauss	4	13,3%
Wegener granulomatosis	2	6,7%
SLE	8	26,7%
Behcet disease	15	50,0%
Secondary vasculitis	1	3,3%

3. Response and evolution:

We defined response when patient's presents a remission of disease, while no response include patient who presented a relapse during its follow up or aggravation of preexisting lesions.

In terms of response we noticed that 26 (86, 7 %) patients out of 30 who received immunotherapy responded favorably to treatment, against 41 (47, 12%) out of 87 of patients under immunosuppressive treatment responses (p=0,001).

We had 6 cases of death in control group against 1 in the immunotherapy group.

3.1 Uveitis :

12 patients,that so 80% , of uveitis (n=15) that were treated with immunotherapy responsed to treatment , while we found that only 25, that so 40 % , had a remission under immunosuppressive (n=63) (p=0,017).

3.2 Renal vasculitis:

Out of 8 Patients with renal involvement we documented 4 patients that had received immunotherapy against 4 patients treated exclusively with cytotoxic molecules. The results were as follow:

- The treated patients with immunotherapy responded to treatment
- 3 patients of the control group responded to treatment (p=0,285)

3.3 Cerebral vasculitis:

In our sample we documented 11 patients with cerebral vasculitis , all of them had secondary lupus vasculitis .the cerebral CT reported different type of radiological lesions .

3 patients received immunotherapy by RITUXIMAB , the results are as follow :

The 3 patients had responded favorably to treatment, against 3 patients out of 8 that received cytotoxic molecules responded to treatment. (p=0,064)

4. Side effects:

46% of patients among the group that was treated with immunosuppressive treated had an infectious episode either during induction with cyclophosphamide or maintenance treatment , where only 33 % had infectious complication(p=0,437).

Lymphopenia was reported in only 2 patients (6,66%) in the immunotherapy group , while it represent 22% in the control group(p=0,09).

	immuotherapy	Cytotoxic molecules	P value
n(%)	30 (20,18%)	87 (79,81%)	
Age (mean)	40	36	0.089
Sex(%male)	43,3% (n=13)	59,7% (n=52)	0.118
females	56,7% (n=17)	40,22% (n=35)	
Response			
Favorable	86,7% (n=26)	47,12% (n=41)	0.0001
Relapsed	13,3% (n=4)	44,82% (n=39)	
Uveitis	80% (n=12)	39,6% (n=25)	0,017
Cerebral vasculitis	100%(n=3)	37,5%(n=3)	0,064
ANCA vasculitis(n= responded)	85%(n=6)	77,7%(n=7)	0,687
Side effects			
lymphopenia	6,6% (n=2)	19,5% (n=17)	0.09
Neutropenia	0% (n=0)	12,6% (n=11)	0.041
Infection	33,3% (n=10)	46% (n=36)	0.437

Table 22: comparative table of patients treated with immunotherapy and patients with cytotoxic molecules

DISCUSSION

Many studies attempted to exam the efficacy of immunotherapy in autoimmune diseases. In this study we compared patients that were treated with immunotherapy to those of the international studies.

I. BEHCETS' DISEASE: INFLIXIMAB

	Our study (N=15)	VALLET and all(multicenter study)[46] n=77
Age (median)	34	32
Sexe: -male	10(66,6%)	42 (55,3%)
Manifestations :		
-articular	6	11
-intestinal	0	6
-muco-cutaneus	15	15
-ocular	15	56
-Retinal vasculitis	11	39
Anterior treatment :		
-AZA	10	25
-CYC	10	22
-MTX	1	14
-MMF	1	6
Indication for Infliximab :		
-refractory BD	12	59
-severe BD	3	
Therapeutic response	94%	96,3%

Table 23: comparative table between our population and the vallet of patients diagnosis with behcet's uveitis

In our study , we found in the group of patients with behcet's diseases that males are the predominant than female with 66,6% , which is in accordance with the study of Valets and all where males represent 55,3% and most patients 41,9% were north Africans. In terms of age, there was no difference between our study and the study of Valet and all.

We noticed no difference of response in our study's and Vallet et al. Which proves the superiority of infliximab in the treatment of uveitis in patients with behcet's disease.

Vallet and al reported in their study that retinal vasculitis was a negative response factor. In our study we documented 11 patients with retinal vasculitis of whom only one patient had not responded to Infliximab (Table 24).

II. IMMUNOTHERAPY EFFICACY :RITUXIMAB

	Our study (n=15)	Smith et al[47] (n=22)	RAMOS-CASAL43[43] al(n=196)	J-E Gottenber et al44[44] (n=43)
-Autoimmune diseases:	Lupus and vasculitis	AAV and lupus	Various disease	Various diseases
-indication:				
*severe	5			
*refractory	9	22	189	39
-RTX regimens :				
*375 mg/m2/week (x4)	15(100%)	22(100%)	169(86%)	35
*1g/15 days (x2)			27 (14%)	5
-Response :				
*responded	14(93,3%)	21(95%)	150(77%)	30(70%)

*No response	1(6,7%)	1	24(23%)	10
-death :	1		6	
Previous therapies :				
- Corticosteroids	15		182 (93%)	
- Cyclophosphamide	4		120 (61%)	
- Methotrexate	4		62 (32%)	
- Azathioprine	5		48 (24%)	
- Other therapies	1		14 (7%)	
Vasculitis : (n=)	(n=7)	(n=11)	(n=19)	(n=5)
-Overall response:				
*TR	6(85%)	10(90%)	13(68%)	2
*NTR	1	1	6(31%)	3
-Overall response by disease:				
*Wegener'sgranulomatosis	½		12/17(71%)	1/1
*Microscopic polyangitis			1/2 (50%)	
*churg et strauss	4/4			
*vascularite nephritis	1/1			
- Pulmonary involvement	3/3		11/14(79%)	
- Renal involvement	3/3		2/2 (100%)	

Table 24: comparative table between our patient treated with RITUXIMAB and other studies

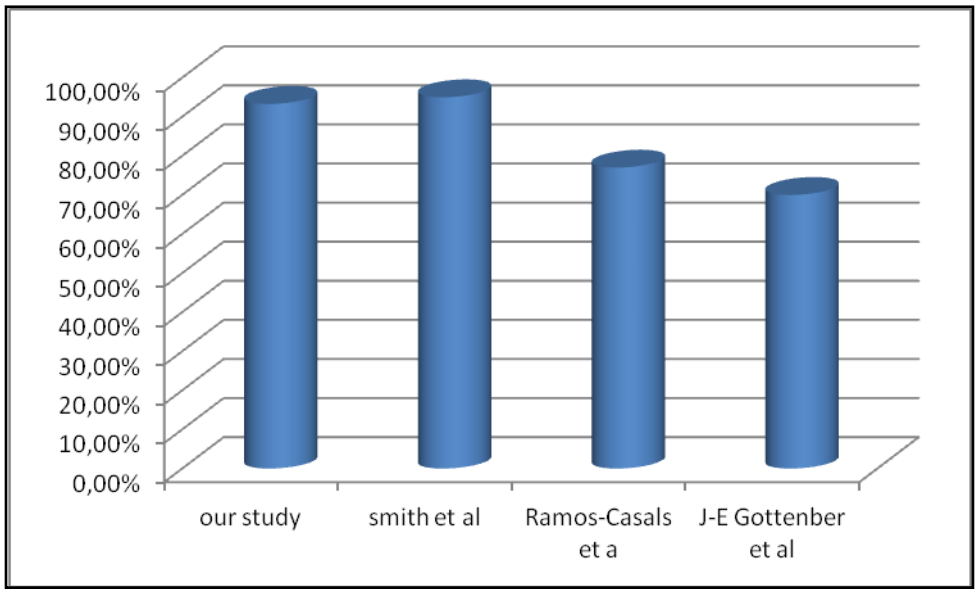


Figure 34: therapeutic response to immunotherapy

Thirty patients had received immunotherapy in our study , 15 of them were treated with Rituximab. The main indication was refractory disease (relapse or no response to previous treatment).

The main pathologies found were lupus (n=9) and vasculitis (n=7). Therapeutic response to Rituximab was at 93,3% , which supports the results of Smith et al showing a rate of response of 95% .

In studies about the efficacy of Rituximab in various autoimmune diseases, the rate of therapeutic response was 77% and 70 % in RAMOS-CASAL et al and Gottenber et al respectively (Figure33).

This low rate could be related to the fact that they included varieties of autoimmune diseases. Moreover, all of our patients and those of smith et al were treated with the Rituximab regimens 375mg/m²/week, whereas only 14% in the studies of Gottenber et al et Ramos-casal et al(Table 25).

1. Efficacy in SLE:

In our study , we documented 8 patients with SLE and treated with Rituximab . All of them (100%), responded to treatment with a median follow-up of 14 months . The rate of response was higher than other study .The lowest rate was that reported by smith et al, 50% of patients responded with a median follow-up of 12 months. The rate of response in general was around 50 to 70% in many studies (Table 26).

1.1 Response by Organ involvement:

In terms of organs involvement, our patients had arteritis, nephritis and cerebral vasculitis secondary to lupus. All these patients responded to rituximab with favorable evolution and disease control (Table 26).

Our findings were higher than the results of Ramos-casals et al where arthritis, CNS and nephritis had response higher than 70% (Figure 34).

LED :	Our study (N=8)	Smith et al (N=11)	RAMOS-CASAL (N=105)	J-E Gottenber (N=13)
-Overall response :				
*TR	8 (100%)	6	81(77%)	9
*NTR		5	24 (23%)	4
-Organ-specific response:				
*Arthritis	4/4		7/9 (78%)	
*CNS involvement	3/3		5/6 (80%)	2/4(patients)
*Nephritis	1/1		17/23	

Table 25: comparative table of organ and response to immunotherapy

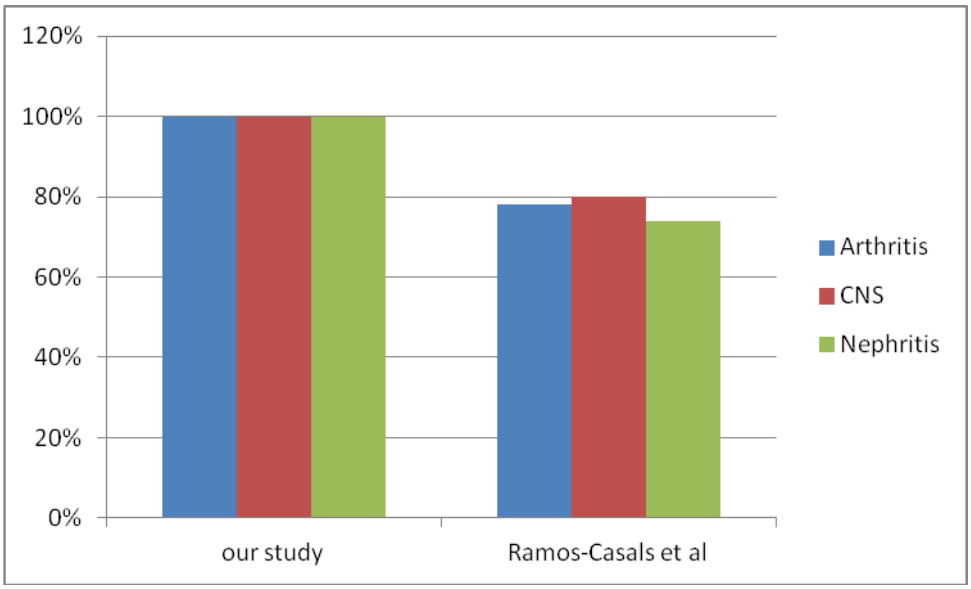


Figure 35: comparative histogramme of response to immunotherpay by organ between our study and the study of RAMOS-CASAL

2. Efficacy in vasculitis:

Our study and that of smith et al reported high rate of response among ANCA vasculitis. While lower response was reported by Ramos-casal et al and the study of gottenber et al, with 68% and 40% respectively. This finding support the RAVE study proven that Rituximab is better in patients with relapse than after first diagnosis, as 5 of our patients received Rituximab as second line treatment.

Out of 2 patients diagnosed with Wegener granulomatosis , only one responded to Rituximab while the other patient had severe form and died due to pulmonary embolism . 75% of patients diagnosed with Wegener granulomatosis in the smith et al study responded well to Rituximab .

In terms of renal lesions in vasculitis the rate of response was 100% in our study as it was the case for Gottenber et al (Table 25).

III. SIDE EFFECTS OF IMMUNOTHERAPY:

Immunotherapy has emerged as an effective therapeutic tool for autoimmune diseases, not only for the high rate of response among cytotoxic refractory disease but also for tolerance and less side effects observed by variety of studies .

Our study reported the highest frequency of adverse events with 43% while in many others studies the rate was between 16 % and 27%.

Infection was reported by Ramos-Casals et al in two different studies as the frequent adverse event with 17,1% and 12%. These were predominantly mild, involving the respiratory and urinary tracts, and were caused by common microorganisms.

Our study found that 33,3% had an infectious complication during their treatment (Table 27).

Respiratory infections are the most frequent among drug receivers with 26,6% higher than 5% in the study of Ramos-Casals et al, While there was no difference between our studies in term of urinary tract infection which represent 3%. Many other adverse events where observed in the reported studies but not in our study such as Neoplasia.

	Our study (n=30)	Ramos-Casals (2008)[45] (n=1370)	Moiseev SV et al[48] (n=107)	Ramos-Casals et al(2010) (n=193)
Received molecules	Rituximab Infliximab	infliximab, rituximab, etanercept, anakinra, adalimumab	Rituximab Infliximab	Rituximab
Rate of adverse events	13(43,3%)	368 (26.9%)	22(20,6%)	33 (16%)
Infections	10(33,3%)	234 (17.1%)	2 (severe infection)	24 (12%)
Hematology	3(24%)		2	2 (1%)
Infusion reaction	3		2(severe infusion reactions)	7 (4%)

Table 26 : comparative table of side affects between our study and others studies

CONCLUSIONS

Upon the previous results we can conclude that in our population sample patients treated with immunotherapy responded well to treatment with significant evolution, in comparison to the control group treated exclusively with cytotoxic drugs.

Less side effects were observed in the population treated with immunotherapy. However, it's hard to correlate the occurrence of these side effects with immunotherapy since most patients received cytotoxic drugs, especially Azthioprine for maintenance therapy.

The rate of serious Adverse Events, mainly infusion Adverse Events and infections during treatment with Infliximab, Rituximab, were shown to be relatively low in patients with different autoimmune diseases. At the same time, the use of biological agents could lower autoimmune diseases activity in the presence of severe visceral injuries refractory to conventional immunosuppressive therapy.

SUMMARY

Introduction: autoimmune diseases are a heterogeneous group of diseases, with diverse clinical manifestations, related to the lost of immunological self tolerance associated

with a host directed immune response. These diseases represent a major clinical problem because of their chronicity and poor therapeutic tools. However in the last decades great advances has been achieved and new therapies have emerged, mainly immunotherapy, owing to the better understanding of the patho-physiological mechanisms behind the distorted immune reaction.

Aim: the aims of these thesis are to overview the latest understanding of the mechanisms that underlies autoimmune diseases, and mainly to present the immunotherapeutic tools and their molecular targets . In addition to highlight the experience of the department of internal medicine in CHU HASSAN II Fez in terms of use of immunotherapy for patients diagnosed with vasculitis, to verify whether immunotherapy is superior to the cytotoxic molecules in treating vasculitis.

Patients and methods: This is a retrospective, descriptive, comparative analysis study performed at the department of internal medicine in CHU HASSAN II Fez from January 1st 2012 to march 31st 2017 involving cases diagnosed with vasculitis in the department.

The study includes 117 consecutive patients diagnosed with vasculitis with 30 cases receiving immunotherapeutic molecules.

Results: The two groups are comparable in term of age, sex, therapeutic response and side effects development . we noticed that 26 (86, 7 %) patients out of 30 who received immunotherapy responded favorably to treatment, against 41 (47, 12%) out of 87 of patients under cytotoxic molecules treatment responses (p=0,001). RITUXIMAB was used to treat secondary vasculitis to SLE and others systemic vasculitis in 15 patients , that so 50% , while INFLIXIMAB was used in patients diagnosed with behcet's uveitis 50% . We had 6 cases of death in the group that received cytotoxic molecules against 1 in the immunotherapy group.

Treatment side effects are higher in the group that had received cytotoxic molecules for treatment , with 46% of patients among the group that was treated with immunosuppressive treated had an infectious episode either during induction with cyclophosphamide or

maintenance treatment , where only 33 % had infectious complication(p=0,437). hematological anomalies were mainly neutropenia , found in 12,6% (n=11) in the control group , and Lymphopenia , reported in only 2 patients (6,66%) in the immunotherapy group , while it represent 22% in the control group(p=0,09).

Conclusion:

Based on the results of our study, in our population patients that received immunotherapy responded well to treatment with significant evolution in comparison to the control group that had received exclusively cytotoxic molecules . we conclude That immunotherapy is an effective therapeutic tool for vasculitis With promising results and Less side effects , indicating a major need for their availability and used mainly as second line for treatment vasculitis.

RESUME

Introduction : les maladies auto-immunes sont des groupes hétérogènes de maladies, avec des manifestations cliniques diverses, liées à une perte de tolérance immunitaire au soi associée à une réponse immunitaire dirigée contre l'hôte. Ces maladies représentent un problème clinique majeur en raison de leur chronicité et la limitations des outils thérapeutiques ayant des effets secondaire très fréquentes . Cependant, au cours des

dernières décennies, de grandes avancées ont été réalisées et de nouvelles thérapies sont apparues, principalement l'immunothérapie, grâce à une meilleure compréhension des mécanismes patho-physiologiques à l'origine de la réaction immunitaire inapproprié .

Objectives : Le but de cette thèse est de présenter les dernières connaissances sur les mécanismes qui sous-tendent les maladies auto-immunes, et principalement de présenter les outils immuno-thérapeutiques et leurs cibles moléculaires. En plus de souligner l'expérience du département de médecine interne au CHU HASSAN 2 Fez en termes d'utilisation de l'immunothérapie chez les patients diagnostiqués avec une vascularite, de vérifier si l'immunothérapie est supérieure à la molécule cytotoxique dans le traitement de la vascularite.

Matériel et méthodes: Il s'agit d'une étude rétrospective, descriptive et comparative réalisée au sein du service de médecine interne à l'hôpital universitaire Hassan II de Fès du 1er janvier 2012 au 31 mars 2017, portant sur des cas de vascularite diagnostiqués dans le département.

L'étude comprend 117 patients consécutifs diagnostic avec vascularite. 30 cas ont reçu des molécules immu- thérapeutiques.

Résultats : Les deux groupes sont comparables en termes d'âge, de sexe, de réponse thérapeutique et de développement d'effets secondaires. nous avons remarqué que 26 (86, 7%) patients sur 30 ayant reçu une immunothérapie répondaient favorablement au traitement, contre 41 (47, 12%) sur 87 des patients traités par des molécules cytotoxiques (p = 0,001). RITUXIMAB a été utilisé pour traiter la vascularite secondaire à SLE et d'autres vascularites systémiques chez 15 patients, soit 50%, tandis que l'INFLIXIMAB a été utilisé chez les patients ayant reçu un diagnostic d'uvéite de Behcet à 50%. Nous avons eu 6 cas de décès dans le groupe ayant reçu des molécules cytotoxiques contre 1 dans le groupe immunothérapie.

Les effets secondaires du traitement sont plus importants dans le groupe ayant recu des molécules cytotoxiques pour traitement, 46% des patients traités par immunosuppresseur ayant un épisode infectieux lors de l'induction par cyclophosphamide ou traitement

d'entretien, où seulement 33% avaient une complication infectieuse (p. = 0,437). les anomalies hématologiques étaient principalement des neutropénies, retrouvées chez 12,6% (n = 11) dans le groupe témoin, et Lymphopénie, rapportées chez seulement 2 patients (6,66%) du groupe immunothérapie, alors qu'elles représentaient 22% dans le groupe témoin. (p = 0,09).

Conclusion: D'après les résultats de notre étude, dans notre population les patients ayant reçu une immunothérapie ont bien répondu au traitement avec une évolution significative par rapport au groupe témoin qui avait reçu exclusivement des molécules cytotoxiques, Nous concluons que immunothérapie est une thérapeutique efficace pour les vascularites Avec des résultats prometteurs et moins d'effets secondaires, indiquant un besoin majeur pour leur disponibilité et leur utilisation principalement comme deuxième ligne pour le traitement des vascularites .

ملخص

مقدمة: أمراض المناعة الذاتية هي مجموعة من الأمراض غير المتجانسة، بأعراض سريرية مختلفة، تتعلق بفقدان القدرة على التحمل المناعي للذات وتكون مرتبطة باستجابة مناعية ضد المضيف. وتشكل هذه الأمراض مشكلة سريرية كبيرة بسبب زمانتها ومحدودية الأدوات العلاجية وما يترتب عن ذلك من آثار جانبية متكررة. إلا أنه تم إحراز تقدم علاجي كبير خلال العقود الماضية لاسيما مع ظهور العلاج المناعي، بفضل فهم أعمق لآليات فيزيولوجيا الأمراض المسؤولة عن الاستجابة المناعية غير المناسبة.

الأهداف: تهدف هذه الأطروحة إلى تقديم أحدث المعارف حول الآليات الكامنة وراء أمراض المناعة الذاتية، وهي تهدف أساسا إلى تقديم الأدوات المناعية العلاجية والجزيئية. بالإضافة إلى تسليط الضوء على تجربة مصلحة الطب الباطني بالمستشفى الجامعي الحسن 2 بفاس، من حيث استخدام العلاج المناعي على المرضى المصابين بالتهاب الأوعية الدموية، للتحقق من فعالية العلاج المناعي مقارنة مع الجزيئة السامة للخلايا في علاج التهاب الأوعية الدموية.

الوسائل والطرق المعتمدة: هذه دراسة استعادية وصفية ومقارنة أجريت داخل مصلحة الطب الباطني في مستشفى الحسن الثاني الجامعي في فاس من 1 يناير 2012 إلى 31 مارس 2017 فيما يتعلق بحالات التهاب الأوعية الدموية التي تم تشخيصها في المصلحة.

وتضمنت الدراسة 117 مصابا بالتهاب الأوعية الدموية. 30 حالة منهم تلقت علاجا بالجزيئات المناعية.

النتائج: المجموعتان قابلتان للمقارنة من حيث العمر والجنس والاستجابة العلاجية وتطوير الآثار الجانبية. لاحظنا أن 26 مريضا من أصل 30 (86.7 ٪) تلقوا العلاج المناعي استجابوا للعلاج، مقارنة مع 41 مريضا من أصل 87 (47.12 ٪) تلقوا العلاج بالجزيئات السامة للخلايا

($p = 0.001$). استعمل الريتوكسيماب في علاج التهاب الأوعية الدموية الناتجة عن التصلب الجانبي الضموري وكذا في علاج أنواع التهاب الأوعية الدموية الأخرى عند 15 مريضا، أي ما يقارب 50٪ من الحالات، في حين تم استخدام الإينفليإكسيماب في علاج المرضى الذين حصلوا على تشخيص التهاب القزحية – (Behcet) عند 50٪ من الحالات. لاحظنا أيضا وجود 6 وفيات في المجموعة التي تلقت العلاج بالجزيئات السامة للخلايا مقابل حالة وفاة واحدة في مجموعة العلاج المناعي.

وبالنسبة للآثار الجانبية للعلاج فقد كانت أكبر في المجموعة التي تلقت العلاج بالجزيئات السامة للخلايا، حيث أن 46٪ من المرضى الذين خضعوا للعلاج المناعي أصيبوا بحلقة معدية عند دخول دواء السيكلوفوسفاميد أو الأدوية المكملة، فقط 33٪ منهم أصيبوا بمضاعفات معدية ($p = 0.437$).

كما نذكر أن المشاكل الدموية كانت تتمثل أساسا في نقص الكريات البيضاء (العدلات)، الشيء الذي لاحظناه عند 12.6٪ من الحالات (ن = 11) في المجموعة الضابطة، ونقص في عدد الخلايا اللمفاوية عند مريضين فقط (6.66٪) من مجموعة التداوي بالعلاج المناعي، في حين لوحظ نقص عدد الخلايا اللمفاوية عند 22٪ من الحالات في المجموعة الضابطة. ($p = 0.09$).

خاتمة: حسب نتائج دراستنا: لوحظ استجابة كبيرة للعلاج من قبل المرضى الذين تلقوا العلاج المناعي مع فارق كبير مقارنة مع المجموعة التي خضعت للعلاج بالجزيئات السامة للخلايا، نخلص إذن إلى أن العلاج المناعي هو علاج فعال لالتهاب الأوعية الدموية بنتائج واعدة وآثار جانبية قليلة، مما يدل على ضرورة توفره واستخدامه كحل ثان لعلاج التهاب الأوعية الدموية.

ANNEXE I: FICHE D'EXPLOITATION

§ IDENTITé

$-Nom et prenom du malade :

……

$- IP :

……

$ AGE : 16 à 29 ans ☐ 30 à 49 ans ☐ 50 à 64 ans ☐ 65 ans et plus ☐

$- SEXE : - Homme ☐ -Femme : ☐

$-ORIGINE : - FES : ☐ -HORS FES ☐ ……

$-ATCD :

-

familiaux :……

……..

-personnels : HTA : ☐ -infectieuse : Tuberculose ☐

- DIABETE : ☐ autres ATCD infectieuse :……

-cardiopathie ☐

autres ……☐……

$ -COUVERTURE SOCIALE : - CNOPS ☐ -CNSS ☐

-RAMED ☐ - AUTRE ☐ ……

§ - DIAGNOSTIC :

-PERIARTERITE NOUEUSE (PAN) ☐

-POLYANGEITE MICROSCOPIQUE ☐

-GRANULOMATOSE EOSINOPHILIQUE AVEC POLYANGEITE ☐

-GRANULOMATOSE AVEC POLYANGEITE ☐

-BEHCET ☐

- uveite ☐

-LED ☐

-AUTRE ……

$- CRITERE DIAGNOSTIC :

……
……
……
……..

§ PRONOSTIC : -BON ☐ -mauvais ☐

§ BIOLOGIE :

$-Bilan inflammatoire : VS : -acceleree ☐ - NON acceleree ☐

$- NFS : lymphopenie ☐ - hyperleucocytose ☐

$- Bilan hepatique : ASAT : …… Bilirubine totale :……..

ALAT :……. Bilirubine conjugee :…….

$-Fonction rénale : ☐ normal ☐ anormal

- Uree : ……

-Creatinine : ……

-proteinurie de 24h :……..

$- Bilan infectieux : CRP :……..

Bk crachat :

Serologie :

HVB : positif : ☐ negatif : ☐

HVC : positif ☐ négatif ☐

HIV : positif ☐ negatif ☐

$- Histologie : PBR: ……

$- RDIOLOGIE : - RX poumon : normal anormal

-ETT : normal anormal

-ECHO abdomino- pelviens : normal anormal

-SCANNER CEREBRAL: normal anormal

- IRM cerebral : normal anormal

- Angio- scanner : normal anormal

$ Examen ophtalmologique :……

§TRAITEMENT :

$-Indication :

$-lieu :- Intra hospitalier ☐ -ambulatoire ☐

$-Moyen :

*Corticotherapie : ☐

* bolus : ☐

* voie orale

* posologie

……..

* Duree : ……☐……..

* IMMUNOSSUPPRESSEURS :

- cyclophosphamide ☐ -MMF :☐

- azathioprine ☐ - methotrexate ☐

$-POSOLOGIE : ……..

-NOMBRE DE CURE :……..

-DUREE :…….

*-Immunotherapie ☐

$ - Indication de l'immunothérapie :

……..

$- MOLECULE :

$ Rituximab ☐ - tocilizumab ☐

$ ANTI TNF ☐ - immuoglobuline ☐

$ PLASMAPHERESE ☐

$ AUTRE ☐ ……

$-POSOLOGIE : ……..

-NOMBRE DE CURE :……..

-DUREE :…….

§ -REPONSE :

- favorable ☐

- duree de remission :

- defavorable ☐

- intervalle de rechute : ……..

§ complication :

$-cutaneo-muqueux :

-allergique : ☐

Autre :…….

$ -infectieuse :

-bacterienne :…….

-virale : …….

-fungique :…….

$-HEMATOLOGQUE :

-leucopenie ☐

-lymphopenie : ☐ -neutropenie ☐

-thrombopénie ☐

- Anemie ☐

$- AUTRE : …….

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