

Autoimmune bullous disease medications (taken from the 19/11/2017 presentation of Dr. Le Roux-Villet delivered during the training seminar on "Patient bridging")

The information about these medicines is not exhaustive but provides patients with some answers to their most common questions.

1. VOCABULARY most commonly used
2. LIST OF THE MOST COMMON MEDICATIONS
3. CORTISONE = CORTICIDE = CORTICOTEROID THERAPY
4. DISULONE® = DAPSONE
5. SALAZOPYRINE® = SULFASALAZINE
6. COLCHICINE
7. TETRACYCLINS
8. CONVENTIONAL IMMUNOSUPPRESSANTS
9. MABTHERA® = RITUXIMAB -
10. XOLAIR® = OMALIZUMAB

1. VOCABULARY most commonly used

A – Different administration routes for treatments:

1) treatment through systemic route = systemic treatment ≠ topical treatment

General/systemic treatment: goes through the blood

- Per os = taken orally or by mouth (tablets / capsules ...): treatment that is swallowed
- Intravenous injection: by perfusion/infusion/drip = parenteral route
- Subcutaneous or intramuscular injection (eg vaccines): injection under the skin – the product is then absorbed and has an effect in the whole body

2) topical treatment

- On the skin (= cutaneous) or on the genital and anal mucous membranes: creams / ointments
- In the eye (= ocular or ophthalmic): eye drops/collyrium
- For the mouth (= oral or stomatological): mouthwashes (or sometimes adhesive ointments)

B – What is an adjunct treatment/therapy?

Adjunctive therapy = adjuvant

It is a treatment intended to supplement the action of the main treatment but is not a cure for the illness in itself.

It is therefore prescribed at the same time as the main treatment. If the adjunctive treatment is a local/topical treatment, its rapid action can relieve some symptoms while waiting for the main treatment to kick in. It is sometimes even prescribed while waiting for certain test results, before prescribing the systemic treatment.

WARNING: local/topical treatments/therapies = adjunctive treatments, most often

Exception:

The topical corticosteroid (Clarelux® or Dermoval® or Diprolene®) in bullous pemphigoid is used as a main treatment and even has a small systemic action (= general)

- it's the strongest available on the market

- it is used in high doses (several tubes at a time)
- at the beginning, it is used daily
- on a skin whose barrier function is not effective: blood passage

C – Different phases of treatment:

Depending on the type of disease and the chosen therapy, different treatment phases are often referred to:

- The attack phase: the goal is to achieve the absence of outbreak of new lesions (blisters or erosions) and a +/- complete cure of the initial lesions. Duration: several weeks
- The decrease phase of the treatment doses: +/- fast decrease of treatments aiming to reach a minimal effective dose. Duration: several months
- The maintenance phase: maintaining a minimal effective treatment (no new lesions), so that there are minimal secondary effects. +/- long duration, a few months – life, depending on the disease

D – Vocabulary: the CBC

Complete Blood Count = CBC

Hemoglobin level: hemoglobin is the carrier of oxygen from the lungs to the organs: the amount of hemoglobin in the blood is therefore a reflection of the ability to oxygenate organs

MCV: Mean Corpuscular Volume = size of the blood cells (interesting to know to find out the cause of an anemia)

Leukocytes: total number of white blood cells (these are part of the immune system)

- Polymorphonuclear/Polynuclear/Neutrophils: in the forefront in case of infection, ability to phagocytize, maintain inflammatory reaction
- Polymorphonuclear/Polynuclear/Eosinophils: increased levels in Bullous Pemphigoid and allergies
- Lymphocytes: delayed immune reaction, 2 major types: T lymphocytes (mostly) and B

Platelets: role in coagulation / no involvement in AIBD

E – Molecule and Trade name:

It may be surprising to hear 2 different names for the same single drug: it is common for one drug to be named by the name of its active molecule or by its commercial name. In writing, the symbol ® is attached to the commercial name. Example: rituximab or Mabthera®.

2. LIST OF THE MOST COMMON MEDICATIONS

A – Anti-inflammatory ≠ of those conventionally used for joint pain (for ex Voltarene® / Profenid®).

The anti-inflammatories used in AIBD are:

- corticosteroids = cortisone = corticotherapy / locally: topical corticosteroids
- other anti-inflammatories: Disulone® / Salazopyrine® / cyclins / colchicine

B – Immunosuppressants:

- Endoxan®
- Cellcept®
- Methotrexate®

- Imurel®
- Neoral®
- Corticosteroids

C – Targeted Action = Biological

- Rituximab (Mabthera®)
- Xolair®
- antiTNF

D – Associated Treatments or medications = to improve drug tolerance / according to prescribed medication

- Speciafoldine (for Disulone®)
- calcium / vitamin D (for corticosteroids)
- potassium (for corticosteroids)
- gastric protectors (for corticosteroids)
- vaccines (for immunosuppressants / corticosteroids / rituximab)

3. CORTISONE = CORTICOSTEROIDS = CORTICOTHERAPY

A – Background: See website: <https://cortisone-info.com/en/home/>

This medication is derived from a natural hormone, cortisol, manufactured by the adrenal gland (Nobel Prize of medicine in 1950), initially for the treatment of patients with rheumatoid arthritis.

Cortancyl was approved in 1955 by the AMM (Autorisation de Mise sur le Marché - French equivalent of the FDA approval)!

Prednisone (Cortancyl®) and prednisolone (Solupred®): 4 times the power of natural cortisol (or hydrocortisone)

Methylprednisolone (Medrol®): 5 times the power of natural cortisol

Widely prescribed drug: at least 1% of the French population takes it on a permanent basis (systemically) / and 3% around 70yr

Acts on receptors present in all cells, in variable quantity

B – Properties:

- anti-allergic
- anti-inflammatory: it decreases production of proteins that promote inflammation
- immunosuppressive: it decreases lymphoid tissue mass as well as numbers of B and T lymphocytes, macrophages, mast cells

Main indications of prolonged corticosteroids:

- lung diseases 50%
- rheumatological diseases 20%
- dermatological diseases 10%
- cancer 5%

C – Instructions for use in AIBD:

- Bullous pemphigoid:
 - Oral corticosteroid therapy (dose of prednisone) - $\frac{1}{2}$ mg / kg / day
 - Local/topical corticosteroid therapy – Heavy (if sole therapy) or as an adjunct treatment (if general CT is given)
- Pemphigus
 - General corticosteroid therapy (dose of prednisone) – 0.5 to 1.2 mg / kg / day
 - Local corticosteroid therapy – As an adjunct treatment
- Mucous Membrane Pemphigoid
 - General corticosteroid therapy (dose of prednisone) – rare
 - Local corticosteroid therapy – As an adjunct treatment



D – Cortisol:

- Is a natural hormone
- Is involved in the regulation of many body mechanisms

When we replace this hormone with a more powerful drug, we can disrupt certain mechanisms that were adjusted by cortisol:

- weight
- mood
- bones / muscles
- stomach
- potassium
- resistance to infections
- blood pressure
- glycemia – blood sugar (sugar)
- cholesterol / triglycerides
- skin
- eyes

The effects depend on: doses / duration of treatment / of each patient

Adrenal insufficiency

- resting of the adrenal gland
- more difficult awakening if rest has been long and general

This risk of adrenal insufficiency means that the discontinuation of corticosteroids needs to be gradual because an adrenal deficiency can put life at risk

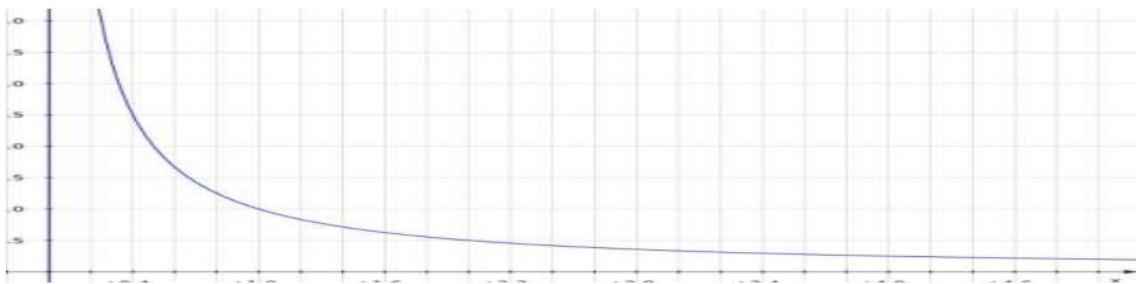
Therefore: a Synacthen test is necessary when treatment is stopped (this test consists of injecting a stimulant to evaluate the ability of the adrenal gland to produce cortisol – this will be measured by a blood test)

Sometimes a supplementation of hydrocortisone tablets is needed

That's why: NEVER STOP THE CORTICOIDS ON YOUR OWN

E – Prescription procedures:

- High dose initially, the decrease is based on protocol or based on monitoring: absence of new lesions and healing of old ones
- Progressive decrease according to a particular curve (the decrease can be accelerated depending on efficacy of adjunct treatment)



Procedures for the clobetasol propionate cream applications (Bullous Pemphigoid):

- daily for about 6 weeks
- 1 day / 2 (every other day) for 4 weeks
- 1 day / 3 (one in three) for the next 4 weeks at least
- 1 time / week for the 4 weeks at least

	Monitoring	Non medicinal therapies	Medicinal therapies
Weight	yes	diet	
Mood/sleep disorder			+/-
Bones	yes	exercise	+
Muscles		Diet / exercise	
Potassium	yes		+/-
Stomach			+/-
Blood pressure	yes	diet	+/-
Glycemia	yes	diet	+/-
Cholesterol/triglycerides	yes	diet	+/-
Infections	yes		vaccinations
Eyes	yes		+/-

Skin			
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Example of therapies associated to corticosteroids :



4. Dapsone - Disulone®

A – Background:

Old medicine:

- 1930s: discovery of its antibacterial activity
- since the 1950s: major treatment in leprosy (in combination)

Two actions:

- antibiotic: especially prevents the multiplication of the leprosy bacteria (Hansen's bacillus)
- anti-inflammatory: interactions with certain white blood cells (neutrophils) hindering their migration and some of their pro-inflammatory functions, without inducing immunosuppression

B – Instructions for use in the AIBD:

- dermatitis herpetiformis
- mucous membrane pemphigoid, adequate in 75 - 85% of cases
- cicatricial pemphigoid, acquired epidermolysis bullosa, linear IgA dermatoses with skin prevalence
- vesiculobullous lupus erythematosus



C – Usual prescription procedures:

- begin with small doses, in general 25 or 50 mg / day, while target dose: towards 150 mg / day
- progressive increase every 15 days
- clinical and biological monitoring

Why such precautions? Dapsone causes two constant phenomena:

- hemolysis
- methemoglobinemia

Hemolysis: decreased life expectancy of red blood cells resulting in the onset of anemia (decrease in hemoglobin levels)

Methemoglobin: incompetent vessel of hemoglobin

Tolerated threshold: 7% of total hemoglobin

D – Contra-indications to treatment:

- anemia
- diseases of the arteries (angina pectoris ...)
- G6PD deficiency (which increases hemolysis)
- severe lung disease ...

E – Regular monitoring:

- clinical: search for shortness of breath, fatigue, pain due to a cardiac origin ...
- Biological:
 - Blood Formula count (CBC) with hemoglobin level
 - reticulocytosis (dosage number of young red blood cells)
 - haptoglobin level
 - methemoglobinemia (to be done only in hospitals because dosage is unreliable if transport is involved)

Expected anomalies:

- decrease in hemoglobin
- VGM increase: size of red blood cells (because younger)
- increase of reticulocytes
- decrease in haptoglobin
- increase in methemoglobinemia

These are DOSE-DEPENDENT abnormalities

Steps allowing a better tolerance:

- very gradual increase of doses
- combination with folic acid supplementation (spéciafoldine®): vitamin assisting the regeneration of red blood cells



F – Rare side effects:

Besides these constant side effects mentioned above, others occur as well:

- sometimes severe "allergy"
- excessive accumulation of iron in the liver

- alteration of the hands & feet small nerves

5. Sulfasalazine - Salazopyrine®

A – Background:

Developed in the 50's for the treatment of rheumatoid arthritis

Currently used in inflammatory bowel diseases (Crohn's disease / Rectocolitis haemorrhagic)

B – Directions for use in the AIBD:

- mucous membrane pemphigoid
- Other AIBD of the non-bullous pemphigoid junction: in addition, or, if contra-indication to Disulone®



C – Usual prescription procedures:

Quasi-constant side effect: gastric discomfort

Prevention:

- very gradual increase of doses (1 up to 6 tablets / day adding 1 tablet / week)
- daily intake breakdown : take tablets in 2 or 3 intakes
- take tablets in the middle of meals

Rare side effects:

"allergy" justifying CBC (Complete Blood Count) monitoring and biological assessment of the liver

6. Colchicine

A – Background:

- Very old medicine originally extracted from the crocus and used since the nineteenth century
- Mechanism of action: decreased mobility and activity of neutrophils
- Usual indication: treatment of gout attack



B – Directions for use in AIBD:

- skin and mucous membrane epidermolysis bullosa

C – Precautions for use:

- Common side effect: diarrhea, hence the possible use of Colchimax®: colchicine + prevention of diarrhea
- Rare risk of allergy
- Watch out for drug interactions

7. Cyclins

A – Background:

Group of medicines: Tetracycline, doxycycline, minocycline

Properties:

- bacteriostatic antibiotic for certain atypical bacteria
- anti-inflammatory (this is a more recent discovery) by action on elimination of neutrophils "used": decreases the duration of the inflammatory reaction
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B – Directions for use in AIBD:

- mucous membrane pemphigoid "light"
- bullous pemphigoid: additional treatment or in very limited forms

C – Precautions for use:

- oesophageal irritation: requires taking it during meals
- photosensitivity: requires taking it at night
- risk of allergy

8. Classical immunosuppressants

A – Background:

- Endoxan® = cyclophosphamide
- Methotrexate® or Novatrex® = Methotrexate
- Imurel® = azathioprine
- Neoral® = ciclosporin
- Cellcept® = mycophenolate mofetil

Indications:

- anticancer treatment (Endoxan®, Methotrexate®)
- prevention of transplant rejection (Imurel®, Neoral®, Cellcept®)
- inflammatory and autoimmune diseases (all)

Cytostatic action: prevents cell division (DNA)

- beneficial for cancer cells that are cells dividing too fast, anarchic
- beneficial because it "calms" the immune system: the T and B lymphocytes divide quickly during the immune reaction to produce antibodies or neutralize infected cells

Immunosuppressive action :

- by cytostatic action (Endoxan®, Methotrexate®, Imurel®)
- by regulation of other T and B lymphocyte systems (functioning and multiplication) (Neoral®, Cellcept®)

B – Directions for use in AIBD:

- severe or resistant mucous membrane pemphigoid (Endoxan® / Neoral® / Cellcept®)
- bullous pemphigoid: failure of corticosteroids alone or cortisone sparing (Methotrexate® / Cellcept®)
- pemphigoid: failure of corticosteroid alone or cortisone sparing (Imurel® / Cellcept®)

C – Precautions for use:

Risks:

- infections
- decrease of red blood cells / platelets
- individual risks (allergies / kidney in the case of Methotrexate®, Neoral® / high blood pressure in the case of Neoral® / liver in the case of Methotrexate® / fertility ...)
- rare risk of cancer induction if prolonged use / if high doses / if other risk factors

How to reduce the risks?

- assess patient's tolerance according to age and medical history
- vaccines
- adjust doses
- monitoring ++
- limit long-term use



9. MABTHERA® = Rituximab - The "REVOLUTION"

A – Background:

A biological drug or bio-drug is a drug whose active substance is a biological substance, ie, a substance that is produced or extracted from a biological source.

Mabthera® or Rituximab is an antibody monoclonal anti-CD20

- the antibody CD20 is present on the surface of B lymphocytes
- it destroys all circulating B-cells
- it has been approved by the FDA (USA) since 1997 for the treatment of non-Hodgkin's B lymphoma ("Lymph node cancers") → "Chemotherapy"
- effective in various autoimmune diseases:
 - cold agglutinin disease
 - autoimmune haemolytic anemia
 - rheumatoid arthritis ...

Mode of action:

- removal of B lymphocytes from the blood +/- BL hidden
- cooperation with other immune cells allows for an immunosuppressive activity, more targeted than with conventional immunosuppressants
- complete elimination of the clone responsible for pemphigus autoantibodies, sometimes

B – Directions for use in AIBD:

- pemphigus
- severe mucous membrane pemphigoid (if conventional immunosuppressive drugs fail or contraindications) or moderate mucous membrane pemphigoid resistant to treatment

C – Precautions and instructions for use:

Due to immunosuppressive potential: risk of infections

→ vaccinations before treatment

→ stop classical immunosuppressants

→ reduce if possible corticosteroids (find the right "timing")

Complete elimination of B lymphocytes: 9-12 months, with gradual increase of their rate; in case of a second treatment, prolonged immunosuppression

Usual dose schedule: 2 infusions of 1g Mabthera® at a 15 day interval (standard pattern)

Premedication: minutes before Mabthera® perfusion

- paracetamol
- antihistamine
- corticosteroid (100 mg)

Purpose of the premedication: to reduce the reactions due to the release of proteins (cytokines) which trigger allergic reactions (itching / hives ... or low blood pressure / discomfort)

D – Biosimilars:

For a drug to be considered a biosimilar of the reference biological product, it must have the same characteristics on the following points:

- active ingredient
- pharmaceutical form
- physico-chemical properties
- biological properties

In addition, clinical trials must have demonstrated its equivalence in terms of therapeutic efficacy and safety.

Biogaran: Truxima® (2 studies, 1 in lymphoma and 1 in rheumatoid arthritis)

Sandoz: Rixathon®

Recent favorable opinion from the HAS (Haute Autorité de Santé) / and from the EMA (European Medicine Agency)

Issue: cost (1g price of Mabthera > 1000 euros)

Usually 20-30% cheaper than reference product

According to the ANSM report on biosimilars:

"If the choice between two biological drugs (reference drug or biosimilar drug) remains free in the absence of a previously identified treatment, it is, however, not desirable for reasons of safety and traceability, to modify the initial prescription, by replacing a specialty drug by another, without guarantee.

In view of the evolution of knowledge and the continuous analysis of data on the efficiency and safety of biosimilars in the European Union, it is clear that a position excluding formally any interchangeability during treatment no longer seems justified.

Thus, if any uncontrolled exchange between biological drugs (biosimilar or reference drugs) is to be avoided, interchangeability may be considered provided that the following conditions are observed:

1. a patient treated with a biological drug must be informed of a possible interchangeability between two biological medicinal products (reference medicine and / or biosimilar medicinal product) and give his agreement ;
2. he must receive appropriate clinical supervision during treatment;
3. traceability of the products concerned must be ensured. "

10. XOLAIR® = Omalizumab

A – Background:

- synthetic antibody that binds to a variety of IgE immunoglobulins and decreases their number (IgE is involved in "allergy")
- Injection

Indications:

- asthma
- chronic urticaria

B – In the AIBD:

- Efficacy in some bullous pemphigoid, at least those with high levels of IgE in the blood
- Rapid and prolonged efficiency, for the moment, on a small number of patients / very good tolerance
- Communication to the national dermatological congress JDP 2018