Evidence-based medicine from a global perspective

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Why do we need evidence- based medicine ?

- highest level of evidence to demonstrate the therapeutic effect of a drug

- RCT > open studies > retrospective studies

What are the limitation of EBM studies ?

- **1- Main limitation:** **very expensive**
- → Most double blind RCT are industry sponsored
- indications
- - focused on diseases usually chosen by industry, rarely by physicians
- - focused on frequent diseases > rare diseases > orphan disease
- - more adapted to developed countries than to developing countries
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- Difficult to convince pharmaceutical companies to support a trial in a rare disease, when a drug is already approved in a frequent disease
- - low financial interest
- - possibility of treatment side effects which could compromise the development of the drug in the indications chosen by pharmaceutical companies
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What are the limitation of EBM studies ?

- **1- Main limitation:** **very expensive**
- → Most of them are industry sponsored
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- Most of them are designed to demonstrate the efficacy of a drug rather than to test a therapeutic strategy. (FDA, EMA approval)
- most drugs are tested versus placebo;
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- Important questions in clinical practce which are rarely assessed:
- - **When using the drug** during the course of the disease ?
- - If different drugs can be used, **what is the optimal dug sequence ?**
- ex adalimumab in HS: likely more effective than demonstrated if used in a therapeutic strategy (surgical removal of abcess, antibiotics…)
- - **What is the optimal treatment duration** ?
- - **what are the cost effectiveness** of therapeutic strategies ?

- The combination of
- - trials only demonstrating the efficacy of drugs
  - absence trial testing a therapeutic strategy

- is responsible for a paradoxical absence of strong evidence from EBM to help dermatologists in their clinical practice

Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis (Review)

Sbidian E, Chaimani A, Garcia-Doval I, Do G, Hua C, Mazaud C, Droitcourt C, Hughes C, Ingram JR, Naldi L,Chosidow O, Le Cleach L

Cochrane review 2018

Conclusion…..

- 109 studies (39,882 randomised participants….)
- review of 495 pages

- **The first choice in conventional systemic agents is still in question** as the limited number of trials assessing conventional systemic agents did not allow us to draw robust conclusions;
- **This is also true for some small molecule treatments and biological treatments…….**

- All that fuss for nothing …..

Or even worse…

- **Serious adverse events**

- « ***We found no significant difference between all of the assessed interventions and placebo*** »
- not relevant: even if SAE related to biologics are not more frequent than in the placebo group, most biologics have rare but specific side effects
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- *"Our analyses strongly suggested that:*
- ***methotrexate had the best safety profile*** *(moderate-certainty evidence),* ***followed by ciclosporin*** *(very low-certainty evidence),* ***certolizumab*** *(moderate-certainty evidence),* ***infliximab*** *(very low-certainty evidence)"*

- Who can believe this conclusion ???

What are the limitation of EBM studies ?

- **1- Main limitation:** **very expensive**
- → Most of them are industry-sponsored

- **Academic studies are difficult to perform**
- needs both public funding + convince companies to provide the tested drug (rituximab in auto immune bullous skin diseases)

- or to test old cheap drugs (methotrexate …), which can be included in the academic funding

What are the limitation of EBM studies

- 2**- Second limitation**:
- - **administrative procedures more and more complex,**
- **longer and longer**
- mean time to start an academic clinical trial after its funding : 2 years

- ⟹ question assessed may not be of interest anymore when the study starts

- exemple: usefulness of combining methotrexate and anti-TNF versus anti-TNF alone to avoid loss of efficacy of anti-TNF agents in psoriasis
- acurate in 3 years ago
- no more interest currently (anti-IL17, anti-IL23-p19 etc…)
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What are the limitation of EBM studies

- 3- **Third limitation**
- - most large studies need collaborative study groups
- do not exist in many countries
- difficult to run
- many academic RCT are underpowered with questionnable results

- **4- 4th limitation**
- - most industry sponsored trials conducted on very selected population (to be homogeneous)
- - in terms of severity
- - often with few comorbidities in order to limit the number of SAE (incitement from both pharmaceutical companies, ethics'committee and national health agencies)
- dozens and dozens of exclusion criteria

- ⟹ conclusion from these very selected populations not always a relevant to « real life patients »

List of exclusion criteria in RCT Rituximab versus cyclophosphamide in severe types of mucous membrane pemphigoid …..

- Patient under 18 years of age or older than 80 years of age,
- Non-consenting patient, or patient who cannot be followed regularly.
- Patients with only MMP sequelae (stenosis, fibrosis, without inflammation or disease activity)
- Patients with Brunsting Perry pemphigoid and exclusive skin lesions without mucosal involvement
- Karnofsky index < 50% (see Appendix 3)
- Known hyper sensitivity to dapsone
- G6PD deficiency (contra indication to dapsone)
- Unstable angina or advanced ischemic cardiopathy (extensive myocardial infarction within the last 3 months or post-infarction heart failure)
- Severe heart failure (NYHA Class III or IV) or severe uncontrolled cardiac disease.
- Uncontrolled cardiac rhythm disorders
- Severe bronchial obstruction
- Past history of malignant disease in the previous 10 years, or current progressive malignant disease, already treated except basal cell carcinoma, and squamous cell cell carcinoma of the skin that have been treated or excised and cured, in situ cervix carcinoma, or any situation in which the oncologist in charge of the patient considers that risk of evolution of severe localisation(s) of MMP is higher than oncologic risk of cyclophosphamide and rituximab.
- Anaemia (haemoglogin < 10 g/dL), neutropenia (<1000/mm^3), lymphopenia (<900/mm^3), thrombopenia (<100 000/mm^3)
- Positive test results for hepatitis B surface antigen (HBsAg), hepatitis B core
- antibody (HBcAb), or hepatitis C virus (HCV) serology at screening
- Liver insufficiency, major renal insufficiency
- Currently active alcohol or drug abuse, or history of alcohol or drug abuse within 24 weeks prior to screening
- Patients with positive blood test for HIV.
- Inherited or acquired severe immune deficiency
- Known active infection of any kind (excluding fungal infections of nail), or
- Infection having required hospitalization, or IV antibiotic treatment within 4 weeks prior to enrollment.
- Past history of severe infection such as fasciitis, osteomyelitis septic arthritis during the year prior to enrollment. Entry into this study may be reconsidered once the infection has fully resolved
- Evidence of any new or uncontrolled concomitant disease that, in the investigator's judgment, would preclude patient participation, including but not limited to nervous system, renal, hepatic, endocrine, malignant, or gastrointestinal disorders
- Any concomitant condition that required treatment with oral or systemic
- corticosteroids within 12 weeks prior to randomisation
- Major surgery within 4 weeks prior to randomisation, excluding diagnostic surgery.
- Patients having received immunosuppressive treatment (such as cyclosporine, mycophenolate mofetil, azathioprine), or any other treatment that might potentially be active on MMP lesions (anti-TNF) within 4 weeks prior to randomisation.
- Treatment with intravenous immunoglobulins , plasmapheresis, or other similar procedure within 8 weeks prior to randomisation
- Previous treatment of MMP with one of the test products: cyclophosphamide or rituximab
- Previous treatment with a B cell–targeted therapy other than rituximab (e.g., anti-CD20, anti-CD22, or anti-BLyS)
- Treatment with a live or attenuated vaccine within 28 days prior to randomisation
- History of a severe allergic or anaphylactic reaction to humanised or murine
- monoclonal antibodies, or known hypersensitivity to any component of rituximab
- Known hypersensitivity or contraindication to cyclophosphamide
- Lack of peripheral venous access
- Women pregnant or lactating, or intending to become pregnant during the study
- Women who are not postmenopausal (≥ 12 months of non–therapy-induced amenorrhea) or surgically sterile must have a negative result from a serum pregnancy test within 1 week prior to randomisation.
- Patients who plan on having children (due to the risk of

What can dermatological societies do to stimulate EBM in profit of patients ?

- **1 - Use incomes from national / international congresses to grant research projects selected by an independent scientific committee**
- ex: French Society of Dermatology gives 60% of its budget (1M€ out of 1.7M€) to fund research projects
- Limitation: since around 30 projects are funded every year, the mean level of funding is rather low 30-40 000 € / project

- → encourage investigators to apply for grants from the National Health agencies

- → small grants can be seen as a limited participationto clinical trials, BUT the scientific support of a national society often helps to further get major grants

What can dermatological societies do to stimulate EBM in profit of patients

- **2 - To convince Pharmaceutical companies to give money to national/internationaly societies, to grant research projects independently selected by the scientific committee of national/ international societies**

- Difficult but not impossible
- Pharmaceutical companies often limit their grants to projects in their field of activity (psoriasis, urticaria, AD, melanoma…)
- They usually prefer to grant a project already identified, rather than giving money first and leaving an independent SC selecting a project
- Some tax benefit procedures can help to convince pharmaceutical companies
- Limitation: time consuming to convince partners
- difficult to organise a durable partnership

What can dermatological societies do to stimulate EBM in profit of patients

- **3 - To support the organisation of collaborative groups of investigators, able to perform multicenter studies**
- Needs to provide facilities for investigators meetings
- (rooms, web conference systems, reimbursement of investigators transportation expenses…)
- needs to fund the collaborative groups
- needs to find a « charismatic » leader to run the group

- <u>Limitation</u>: competition between investigators
- choice of the leader of the collaborative group is crucial

What can dermatological societies do to stimulate EBM in profit of patients

- **4 - To convince pharmacological companies to support trials**
- - rare diseases
- - poorly profitable diseases
- - trials specifically designed for developing countries
- difficult to convince companies to grant studies which are not in their field of activity

- **5 to collaborate with patients' associations to define « high need diseases » and use their lobying ability**

Conclusion

- - Dermatological Societies / Leagues must support clinical trials much more than they do

- - in order to design studies which are not only limited to profitable indications
- - to study clinically relevant issues
- - adapted to the variety of health care systems in different countries
- - propose partnerships with pharmaceutical companies