What`s new in DRESS

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Conflict of interest

• WP is employed by ADR-AC, a company investigating drug hypersensitivity reactions
• WJP was consulting in the last two years for
  – Teleflex
  – ArgenX
DRESS: drug reaction/rash with eosinophilia and systemic symptoms

**Causes:** longer lasting therapy with antiepileptics, antibiotics, etc.
**Time line:** slow start (weeks), lasting for weeks/months
**Skin symptoms:** variable types of exanthems, face swelling, AGEP like,…..
**Organs:** hepatitis, nephritis, pneumonitis, carditis, colitis, meningitis…
**Labor:** atyp. lymphocytes, eosinophilia (~70%)
**Confusion:** different organs affected, recurrence in absence of drug (viral & autoimmune complications) or after applying other drugs (MDH)
Formation of a new antigen (covalent); dose-dependent effect; costimulation needed

Classical immune reaction with antibodies and T cells (Gell/Coombs); Actually mostly NO SYMPTOMS: unresponsiveness, tolerance;

Stimulation of T cells exclusively: \( \rightarrow \) unorthodox activation (like to allo-HLA) results in polyspecificity (high cross-reactivity/heterologous immunity) and high cytotoxicity

HOW: covalent
\( \rightarrow \) IMMUNITY

HOW: Non covalent
WHICH PROTEIN: off target activity
a) TCR/HLA: p-i
b) receptors/enzymes of inflammatory cells: pseudoallergy

\( \rightarrow \) DRUG HYPERSENSITIVITY

«A-p-p» Classification of DHR based on

a) **How drugs bind to proteins &**
b) **to which proteins**

**Allergy**

Formation of a new antigen (covalent); dose-dependent effect; costimulation needed

**Pseudo-allergy**

Drugs bind directly (non-covalently) to receptors & enzymes of effector cells, no real allergy

**Pharmacological interaction of drugs with immune receptors:**

Drugs bind directly (off-target, non covalently) to immune receptors (HLA, TCR)

Classical immune reaction with antibodies and T cells (Gell/Coombs); Actually mostly NO SYMPTOMS: unresponsiveness, tolerance;

Stimulation of T cells exclusively: \( \rightarrow \) unorthodox activation (like to allo-HLA) results in polyspecificity (high cross-reactivity/heterologous immunity) and high cytotoxicity

HOW: non covalent

MRPGPRX2/Mast cells
anaphylaxis/urticaria
Cyclooxygenase↓/Leukotriens ↑
bronchospasm, asthma, urticaria
Bradykinin↑: angioedema

WHAT PROTEIN:

a) TCR/HLA: p-i
b) receptors/enzymes of inflammatory cells: pseudoallergy

\( \rightarrow \) DRUG HYPERSENSITIVITY

How: non covalent

 WHICH PROTEIN:
 a) TCR/HLA: p-i
 b) receptors/enzymes of inflammatory cells: pseudoallergy

\( \rightarrow \) DRUG HYPERSENSITIVITY

*Pichler WJ. The important role of non-covalent drug binding in drug hypersensitivity reactions, Allergy, 2021 May 26*
P-i activated T cells are «abnormal»

- **polyspecific**
  - they react with many different peptides, some T cells even with different HLA (alloreactivity↑).
  - This broad specificity → heterologous immunity;

- **cytotoxic**
- T cell hyperreactivity ongoing (PD1+, CD38+) after stop of drug exposure due to stimulatory interaction with cross-reactive antigens (viral, self-peptide)

→ Chaotic immunity in p-i due to by-passing of «rules» of controlled «normal» antigen driven T cell stimulation: no HLA-restriction, no costimulation by CD4/CD8/LAT engagement, no DC activation/presentation of antigen
DRESS are p-i reaction

- When *investigated*, the T cell reaction in DRESS were *always* identified as p-i: Sulfamethoxazole, carbamazepine, abacavir, lamotrigine, vancomycin, dapsone, allopurinol etc….

- Many severe DHR are HLA-linked: *All* HLA linked DH are due to *direct* drug binding to HLA-proteins (= p-i); (and not to the drug-modified peptide).
DRESS: Clinical course

1. P-i stimulation
2. Expansion of T cells (drug-dependent, cytotoxic, polyspecific: allo-like (GVHD))
3. Symptoms, acute DRESS
4. Virus release / reactivation
5. Autoimmunity
6. MDH (Multiple Drug Hypersensitivity)

1 2: asymptomatic;
3: symptoms, acute DRESS
4, 5: Crossreactivity of p-i stimulated T cells with viral peptides (herpes) & self peptides;
6: new DH caused by other drugs (MDH)
Multiple drug hypersensitivity (MDH)

MDH is a syndrome that develops as a consequence of massive and unorthodox T cell stimulations (p-i, allo-like) during DRESS/severe MPE. It is characterized by new drug hypersensitivity reactions to novel drugs (not structurally related to first DRESS-elicitor); No cross-reactivity. Ca. 20% of patients with DRESS develop MDH
Clinical course/types of MDH

1st drug or drug combination
DRESS, severe exanthem, bullous IgA dermatosis……..
- e.g. CBZ (sequential)

2nd drug or drug combination
Exanthem, DRESS, erythrodermia, agranulocytosis, fulminant hepatitis, necrotizing carditis, SJS/TEN, death …
- e.g. amox (distant)
- Activation/lymphoblasts (years)
- simultaneous (combination therapy)
- together
DRESS
Take home message

– DRESS is the result of abnormal immune stimulations by drugs (p-i; allo-like, similar to gvhd, acute transplant rejection, superantigen)
– It is often not correctly diagnosed as symptoms start late, clinical course is unusual. Symptoms are often mistaken as infection, and new therapy provokes MDH, which is widely unknown
– Often continuous or recurrent symptoms in absence of drug (→ doubt on drug etiology & confusion)
  • Viral release
  • Autoimmunity
  • Multiple drug hypersensitivity
P-i reactions are the main cause of delayed appearing DHR

The symptoms reach from mild to severe; they are dependent on

1) **affinity** of non-covalent drug-immune receptor (HLA, TCR) interactions
2) **dose** & **duration** of drug therapy
3) **type of p-i** (localization of binding site to TCR or HLA) &
4) **type of drug** (some influence on organ manifestation): allopurinol: kidney, lamotrigine: liver; sulfasalazine: lung, etc....

→ mild to severe DHR with drug-dependent manifestation in skin, liver, kidney, lung ...

Mild «rash»  \[\rightarrow\]  MPE  \[\rightarrow\]  DRESS or SJS/TEN
Classification:

P-i:

Covalent-non covalent, late complications of p-i/DRESS:

MDH:

For further insight (literature):
THANK YOU FOR YOUR ATTENTION
Late consequences of p-i activation:

1. High virus load: HHV6, CMV, EBV,.. (just release or reactivation?)

2. Autoimmunity (endocrine, vitiligo)

DRESS: Massive T cell activation targeting many organs

3 - 6 weeks -> >50% of DRESS

6 - 12 weeks -> ~<20% of DRESS
Causes of MDH (1st & 2nd/3rd drug), proven by LTT/Cyto-LTT

**First drug (n=31)**
- 5x: Amoxicillin
- 3x: Sulfasalazine (sulfapyridine/5-aminosalicylic acid), sulfamethoxazole/trimethoprim, phenytoin, carbamazepine, rifampicin, amoxicillin/clavulanic acid
- 2x: Lidocaine
- 1x: Vancomycin, allopurinol, escitalopram, metronidazole, ceftriaxone, cefepime, cefuroxime, piperacillin/tazobactam, isoniazid

**Follow up drugs (2-3rd DHR)**
- 2x Amoxicillin, sulfamethoxazole/trimethoprim, budesonide
- 1x phenytoin, lamotrigine, carbamazepine, triamzolam, amitriptyline, pantoprazole, rifampicin, clindamycin, metronidazole, sulfamethoxazole, ceftobiprole, ceftriaxone, ertapenem, penicillinG, piperacillin/tazobactam, vancomycin, levofloxacin, ciprofloxacin, zonisamid