Biological Therapies-The Advent, Present and Future

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Objective

- Familiarise Health Care Workers with the various indications of Biological Therapies in the Pediatric Population
Outline

- Definition
- History of Biological Therapies
- Rationale for Using Biological Therapies
- Nomenclature of Biological Therapies
- Current Indications
  - Neurology
  - Cardiology
  - Pulmonology
  - Hemato-Oncology
  - Gastroenterology
  - Rheumatology
- The Future
Definition

- Biological therapies can be defined as substances made by, or indeed consisting of, living cells and used for the treatment or prevention of disease.

History

- 1700’s Edward Jenner and the milkmaids.

- Discovery of human blood groups by Karl Landsteiner in 1901 improved safety of blood transfusion.

Overview of Inflammation

Figure 1 Primers of inflammatory cascade [6]
Nomenclature

Monoclonal Antibody

Purple: Human component
Orange: Murine components
Current Indications
Neurology-Intravenous Immunoglobulin (IVIG) in FIRES

Pathophysiology
- Antibody-related encephalitis,
- Aberrations in the Innate Immune System
- Genetic predisposition.

IVIG in FIRES

Table 1

<table>
<thead>
<tr>
<th>Patients with normal intellectual outcome (%)</th>
<th>Median age (range) in normal outcome patients vs cognitive impairment patients or death</th>
<th>Immunosuppressive treatment (%) in normal outcome patients</th>
<th>IS in the patients with cognitive impairment patients or death</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/77 (15.58%) vs 7/6 y-o (range 2–15)</td>
<td>No treatment 5/12 (41.6%) IS treatment 7/12 (58.4%)</td>
<td>IVIG 1/12 (8.3%) MP 2/12 (16.6%) MP + IVI 4/12 (33.3%)</td>
<td>IVIG 11/65 (16.9%) MP 4/65 (6.1%) MP + IVI 11/65 (16.9%)</td>
</tr>
<tr>
<td>2/22 (9.09%) vs 7.5 y-o (range 3–15)</td>
<td>No treatment 2/2 (100%)</td>
<td>Unknown 3/65 (47.2%) No treatment 10/20 (50%) IS treatment 10/20 (50%)</td>
<td></td>
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</tbody>
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and swallowing automatisms (Supplementary Video 1). There was no secondary generalization.

Supplementary material related to this article found, in the online version, at http://dx.doi.org/10.1016/j.seizure.2012.11.006.

CSF analysis showed 6 cells and normal glucose and protein levels. No immunoactivity was detected to intracytoplasmic neural antigens (Hu, Ri, Yo, Amphiphysin) or to surface antigens (NMDAR, LGI1 or other potassium channels), Serological and PCR tests for neurotropic viruses (including herpes group viruses and

These include the so-called febrile infection-related epilepsy syndrome (FIRES), van Baalen et al. and Kramer et al. published the most important series describing this phenomenon to date and outlined the clinical profile of FIRES. Symptoms were most prevalent in patients under the age of 15, and there was a slight male predominance. All patients had suffered an infection in the week prior to the onset of symptoms. Respiratory tract infections were the most common (more than 50%). The natural history of FIRES is typically biphasic, with a seizure-free period between
Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease


ABSTRACT

BACKGROUND
Experimental and clinical data suggest that reducing inflammation without affecting lipid levels may reduce the risk of cardiovascular disease. Yet, the inflammatory hypothesis of atherogenesis has remained unproven.

METHODS
We conducted a randomized, double-blind trial of canakinumab, a therapeutic monoclonal antibody targeting interleukin-1β, involving 30,061 patients with previous myocardial infarction and a high-sensitivity C-reactive protein level of 2 mg or more per liter. The trial compared three doses of canakinumab (50 mg, 150 mg, and 300 mg) administered subcutaneously every 3 months with placebo. The primary efficacy end point was nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death.

RESULTS
At 48 months, the median reduction from baseline in the high-sensitivity C-reactive protein level was 26 percentage points greater in the group that received the 50-mg dose of canakinumab, 37 percentage points greater in the 150-mg group, and 41 percentage points greater in the 300-mg group than in the placebo group. Canakinumab did not reduce Ept levels from baseline.
Pulmonology-Asthma

Chronic inflammation
Remodelling
Pathology

Asthma
Reversible symptoms
Exacerbations
Clinical expression

Variable airflow obstruction
Airway hyperresponsiveness
Physiology
Biological Therapies in Asthma

Biological drugs in asthma treatment

2. Th2 Response

Anti-IL-4 biologies
- Anti-IL-4 monoclonal antibodies
  - Mepolizumab (anti-IL-4)
  - Reslizumab (anti-IL-4)
- Benralizumab (anti-IL-5RA)
- mAbPSC (anti-IL-5R and anti-CCR5 receptor antagonist oligonucleotide)

IL-4/IL-13 antagonists
- Poxetuzumab (anti-IL-4 mAb)
- Atorvastatin (statin drugs for IL-4/IL-13)
- Puriokizumab (IL-4/IL-13 mAb)
- Anti-IL-13 monoclonal antibodies
  - Lebxizumab
  - Ancrumizumab
  - Dalilimuzumab (anti-IL-4Ra mAb)

Anti-IL-9 monoclonal antibodies
- MEDI-522

IL-4 variants
- Pitrakinra
- Ancrumizumab
- Ancrumizumab

IL-5-specific Abs
- Mepolizumab
- Reslizumab
- Benralizumab

IL-5

Eosinophils

T helper 2 (Th2) cells

Neutrophils

Allergens

Dendritic cell (antigen-presenting cell)

IL-17-specific Abs
- Secukinumab
Hemato-Oncology

**T-cell Activation**

- T cell
- CTLA-4
- CD28
- CD80/CD86
- TCR
- MHC
- APC

**T-cell Inhibition**

- T cell
- CTLA-4
- CD28
- CD80/CD86
- TCR
- MHC
- APC

**T cell Remains Active**

- T cell
- CTLA-4
- CD28
- CD80/CD86
- TCR
- MHC
- APC

**YERVOY blocks CTLA-4**
Gastro-enterology-Biologics in IBD

Trends in Pharmacological Sciences
Biological Therapies in Rheumatology

TNF inhibitors
- Infliximab
- Etanercept
- Certolizumab pegol
- Adalimumab
- Golimumab

Other biologic agents
- Anakinra
- IL-1 signaling
- IL-1R
- IL-6
- Tocilizumab
- IL-6 signaling
- IL-6R
- Rituximab
- CD20
- B-cell depletion

Antigen
- MHC
- APC
- CD80 or CD86
- CD28
- Co-stimulatory signal
- T-cell receptor
- T cell
- B cell
- B-cell depletion

Abatacept
Toxicity

- Encephalitis, aseptic meningitis
- Hypophysitis
- Uveitis
- Thyroiditis, hypothyroidism, hyperthyroidism
- Pneumonitis
- Dry mouth, mucositis
- Rash, vitiligo
- Thrombocytopenia, anemia
- Myocarditis
- Hepatitis
- Pancreatitis, autoimmune diabetes
- Adrenal insufficiency
- Nephritis
- Colitis
- Vasculitis
- Enteritis
- Arthralgia
- Neuropathy
Which Biologic do I choose?

- AFASS (Affordable, Feasible, Acceptable, Sustainable, Safe)
- Co-morbidities
- Co-medications
- Patient preference
- Compliance
Pre-biologic precautions

- Vaccination pre-biologic
  - Influenza
  - Pneumovax
  - Hepatitis A & B prn
  - Tetanos prn

- Once on biologic
  - Avoid all live vaccines (yellow fever, VZV, MMR)
  - Yearly influenza?
A next step in adeno-associated virus-mediated gene therapy for neurological diseases: regulation and targeting

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Recombinant adeno-associated virus (rAAV) vectors mediating long term transgene expression are excellent gene therapy tools for chronic neurological diseases. While rAAV2 was the first serotype tested in the clinics, more efficient vectors derived from the rh10 serotype are currently being evaluated and other serotypes are likely to be tested in the near future. In addition, aside from the currently used stereotaxic-guided intraparenchymal delivery, new techniques for global brain transduction (by intravenous or intracerebrospinal injections) are very promising.

Various strategies for therapeutic gene delivery to the central nervous system have been explored in human clinical trials in the past decade. Canavan disease, a genetic disease caused by an enzymatic deficiency, was the first to be approved. Three gene transfer paradigms for Parkinson’s disease have been explored: converting L-dopa into dopamine through AADC gene delivery in the putamen; synthesizing GABA through GAD gene delivery in the overactive subthalamic nucleus and providing neurotrophic support through neurturin gene delivery in the nigro-striatal pathway.

These pioneer clinical trials demonstrated the safety and tolerability of rAAV delivery in the human brain at moderate doses. Therapeutic effects however, were modest, emphasizing the need for higher doses of the therapeutic transgene product which could be achieved using more efficient vectors or innovative carriers. This will require an addressing of pharmacological aspects with attention
Questions
Summary

Figure 1 Primers of inflammatory cascade [6]
Thank You!

Thank you!

ESKERRIK asko!

IGRACIAS!

Merci Beaucoup!

спасибо

Moc děkuji

Ευχαριστώ

Danksagung!