Drug Discovery and Emerging Treatments

Cure JM Family Conference

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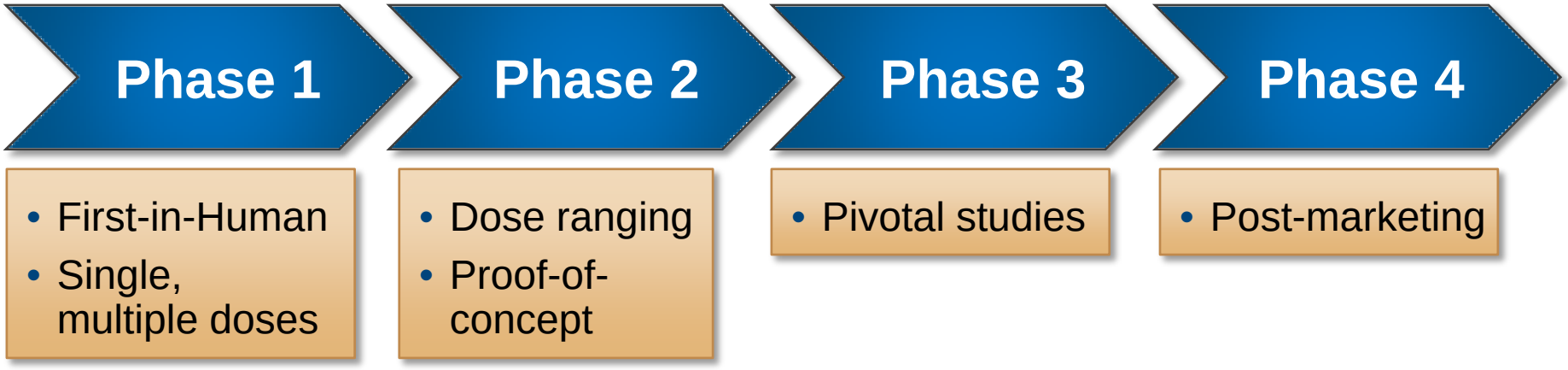
Phases of Therapeutic Trials



- **Phase I:** Establishes that a drug is SAFE to use in a small group of healthy volunteers (10-80) *(70% success rate)*
- **Phase II:** Evaluates efficacy AND safety of drug in larger group of patients that have the disease or condition (often 100-300, can be smaller) *(33% success rate)*
- **Phase III:** Confirms a drug's efficacy and monitors side effects in a larger group of patients (300 to 3,000, for licensure) and conducted at multiple centers *(25-30% success rate)*
- **Phase IV:** Conducted after FDA approval and brought to market to further evaluate long-term side effects

Importance of Volunteering for Trials

- It can take up to 12 years and millions of dollars to get a drug to clinical trials
- Just making it to a clinical trial is extraordinary, especially for a rare disease
- Yet, lack of volunteers in a clinical trial is one of the greatest challenges faced by clinical researchers
- Volunteers are CRUCIAL to get a drug on pharmacy shelves or learn new information about a disease.
  - 85% of all trials are delayed due to difficulties enrolling patients

Challenges: Rare Disease Clinical Trials

- Small population
- Heterogeneous diseases
- Often poorly understood, e.g. natural history
- Lack of drug development precedent,
  lack of pharma interest
- Showing adequate evidence of efficacy with
  limited number of patients available for study
- Relatively few experienced trial sites/investigators
- Preparing patients for trial entry: decrease steroid,
  far out from rituximab, active and stable disease,
  not too much damage (scarring)

Pediatric Legislation: US/European Union Comparison

	FDA Best Pharmaceuticals for Children Act	EU Paediatric Regulation
Development	Voluntary studies	Mandatory (Optional for off-patent)
Timing	End of phase 2	End of phase 1
Reward	6 months market exclusivity on the drug/biologic	6 months patent extension
Drugs (section 505)	Yes	Yes
Biologics	Yes – Most	All
Orphan	Included – FDA may make written request for products with orphan designation	Included
Goal	Pediatric – Specific labeling based on pediatric studies	Pediatric – Specific labeling based on pediatric studies
Decision	FDA	EMA – Pediatric Committee

FDA Programs for Rare Diseases

- Orphan Drug Designation:
  - Rare disease- fewer than 200,000 people in the U.S.
  - 7 years exclusivity (no competition)
  - Tax credit of 50 percent of clinical testing costs
  - Waiver of drug application fees
- Rare Pediatric Disease Priority Review Voucher
  - Sponsor who receives approval of drug for rare pediatric disease may qualify for a voucher for priority review of another application for a different product.
- FDA Orphan Products Grant Program
  - Provide funding for research to assess safety and efficacy of drugs for rare diseases

https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/ucm2005525.htm

FDA Expedited Programs for Serious Conditions

- Treat serious condition, FDA input through development, FDA can be more flexible – single study with supportive evidence
- Fast Track
  - Nonclinical or clinical data demonstrate potential to address unmet medical need
  - Actions to expedite development and review, rolling review, potential priority review
- Breakthrough Designation
  - Clinical evidence indicates the drug may demonstrate substantial improvement on clinically significant endpoints over available therapies
  - Intensive guidance on efficient development, rolling review, potential priority review

FDA Expedited Programs for Serious Conditions

- Accelerated Approval
  - Meaningful advantage over available therapies
  - Effect on surrogate endpoint likely to predict clinical benefit or on clinical endpoint measured earlier that is likely to predict effect on irreversibly morbidity or mortality
  - Post-marketing confirmatory trials required
- Priority Review
  - Significant improvement in safety or effectiveness or a labeling change supplement for a pediatric study
  - Priority review of 6 months (vs. standard 10 month review)

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

Increase in Orphan Drug Approvals has Resulted from FDA Incentives

- 1996 – 57 new drugs approved; minimal orphan drugs
- 2015 – orphan drugs comprised 47% of the FDA approved drugs. 21 of 45 drugs for rare diseases.
- 500 Orphan Drugs approved in 3 decades
  - Positive sides of approvals: Licensure for rare disease indications, insurance coverage for medications, availability of much needed treatments
  - Negative: Some medicines are very expensive
- For myositis – increasing Pharma interest compared to previous decades

Benefits of Volunteering for a Trial

- Access to treatment may not be available outside of trial
- Treatment could be more effective and/or safer than standard treatments and you would be first to benefit- or you may have exhausted standard treatments and this provides a new treatment option
- You will be closely monitored by researchers and might have additional testing
- You will have the chance to see more doctors and learn more about your disease
- Your involvement will help move research forward

Risks of Volunteering for a Trial

- New treatment may not be better than standard treatment
- New treatment may have side effects that researchers did not expect
- You may need additional visits to the doctor and additional tests
- You may not benefit

Seven Current Clinical Drug Trials for JDM

4 JDM trials or combined JDM/DM trials

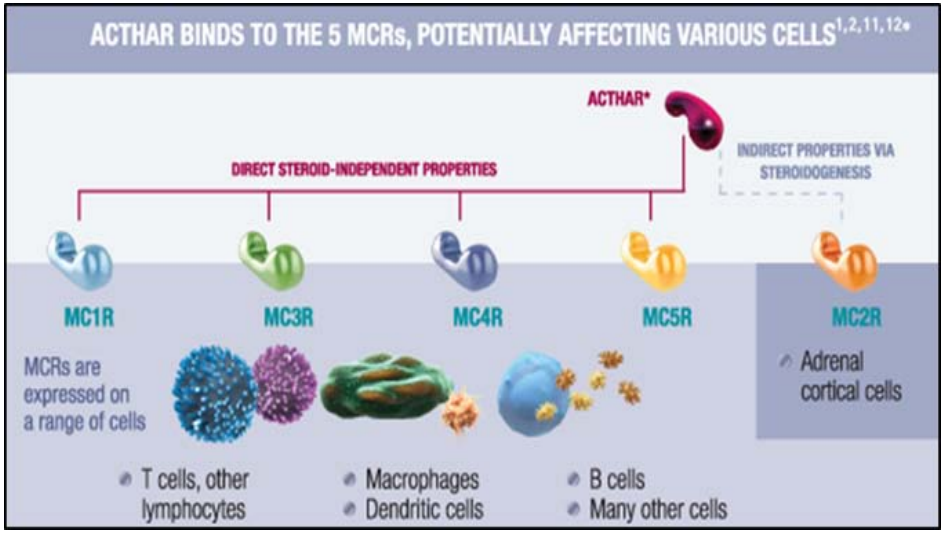
- **Abatacept Trial** in Juvenile Dermatomyositis (AID trial), GWU Myositis Center (NCT02594735)
  - Phase 2, Open Label, SQ treatment, age ≥ 7 years – see handout
- Efficacy and Safety of H.P. **Acthar Gel** for the Treatment of Refractory Cutaneous Manifestations of Dermatomyositis (Acthar Gel) (NCT02245841)
- Compassionate Use Protocol of **Baricitinib** for the Treatment of Autoinflammatory Syndromes, including Severe Juvenile Dermatomyositis (NCT01724580)
  - Oral drug, compassionate use, will close to new patients at end of August- discussed in Main session
- **Sodium Thiosulfate for** Treatment of **Calcinosis** Associated with Juvenile and Adult Dermatomyositis (NCT03267277)
  - Phase 2, Open label, IV treatment, moderate to severe calcinosis and stable myositis, adults eligible (plan to enroll children later) – see handout

Efficacy and Safety of H.P. Acthar Gel for Refractory Cutaneous Manifestions of DM

This study will assess the safety and efficacy of H.P. Acthar Gel (an adrenocorticotropic hormone (ACTH) analogue) for treating cutaneous manifestations in patients with refractory disease (NCT02245841).

Background:

- Long-acting formulation of ACTH, including other pro-opiomelanocortin peptides that may have immunomodulatory properties
- FDA approved for DM/PM, based on limited data



Inclusion Criteria:

- 18 years of age or older with JDM or DM or amyopathic DM
- Active skin disease with a biopsy consistent with dermatomyositis; muscle disease may be active

Study Details:

- Subcutaneous injection twice weekly
- 4 clinic visits to Cleveland Clinic over 6 months with clinical testing, questionnaires and lab draws, including myositis panel, at baseline and 6 months
- Everyone receives the medication (no placebo)
- Medication and clinic visits are free
- $50 stipend per visit

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Seven Current Clinical Drug Trials for JDM

3 DM/PM trials that allow adults with JDM to enroll

- Efficacy and Safety of **Abatacept** in Combination with Standard Therapy Compared to Standard Therapy Alone in Improving Disease Activity in Adults with Active Idiopathic Inflammatory Myopathy (NCT02971683)
  - Randomized controlled trial with placebo group, JDM patients who are adults included with + muscle biopsy or MSA test, SQ treatment, many enrolling centers
- **Tocilizumab** in the Treatment of Refractory Polymyositis and Dermatomyositis (TIM) (NCT02043548) – Aggarwal/Oddis
- A Phase 2a, Double-blind, Randomized, Placebo-controlled Study To Evaluate the Efficacy, Safety, and Tolerability of **Pf-06823859** in Adult Subjects with Dermatomyositis (NCT03181893)
  - See handout – 11 enrolling centers incl JHU, **IFN-β blocker**, skin outcomes/biopsies

Juvenile Idiopathic Arthritis Drug Development

- Number of licensed drugs and biologics for JIA – including Anti-TNFα, IL-1 blocking therapies, Tocilizumab (IL-6R Mo Ab), Abatacept
- Large number JIA Clinical Trials for new biologics and drugs
  - Golimumab (anti-TNFα MoAb), Belimumab (anti-BlyS), Rituximab, Tofacitinib (JAK Kinase inhibitor)
- Importance of JIA trials
  - Dosing and safety established in children with systemic rheumatic diseases
  - Some children with JDM may be “coded” as having JIA and be able to obtain insurance coverage for drugs/biologics licensed for JIA
- Rationale for high number of trials:
  - Higher prevalence of both JIA and adult RA
  - Companies have more incentive to develop medications for JIA versus JM because they will make more money, regulations favor incentives for development for JIA (esp in Europe and for biologics – PREA pediatric reg)

How to Find Out About Clinical Trials

- Check Clinicaltrials.gov website for trials: https://clinicaltrials.gov
  - Search juvenile dermatomyositis or dermatomyositis
  - Observational (natural history studies) also posted
  - Volunteer for a Clinical Trial or research study if it's appropriate for your child and you