Novel treatments for rare rheumatologic disorders: analysis of the impact of 30 years of the US orphan drug act

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Abstract

Background: Rare rheumatologic diseases are a heterogeneous group of conditions associated with high morbidity. As a whole group, rare rheumatologic diseases afflict millions of people demanding for effective therapies. Therefore, we analyzed the impact of the US Orphan Drug Act on the development of anti-rheumatic orphan drugs.

Methods: Analysis of the FDA database for orphan drug designations.

Results: In the last three decades, out of 77 orphan drug designations, 14 orphan drug approvals were granted by the FDA for the treatment of rare rheumatologic disorders, i.e. juvenile idiopathic arthritis (N = 5), cryopyrin-associated periodic syndromes (N = 3), uveitis (N = 3), familial Mediterranean fever (N = 1), anti-neutrophil cytoplasmic antibody-associated vasculitis (N = 1), and xerostomia and keratoconjunctivitis sicca in Sjögren’s syndrome (N = 1). Mean time (standard deviation) from designation to approval was 3.9 (2.81) [range 1 … 12] years. Number of FDA-approved small molecules (N = 6, 43 %) and biologics (N = 8, 57 %) was comparable. Almost every fifth (19 %) orphan drug designation was withdrawn. Despite the rarity of conditions, 13/14 pivotal studies were randomized controlled trials.

Conclusions: Orphan drug development is challenging: thirty years of US orphan drug act supported the development and FDA approval of 14 orphan drug programs with anti-rheumatic compounds for six rheumatologic diseases.

Keywords: Orphan drug act, Orphan drug development, Rare disease, Rare rheumatologic disease

Background

Rheumatologic diseases are associated with high morbidity leading to reduced quality of life, potentially life-long disability, and premature death. Although rare in individuals, as a whole group rare rheumatologic disorders afflict a large group of people [1, 2]. Furthermore, many rare autoimmune inflammatory conditions, such as systemic lupus erythematoses, dermatomyositis, scleroderma, vasculitis, periodic fever syndromes, nonbacterial osteomyelitis, or uveitis can manifest already in childhood. For example, the prevalence of juvenile idiopathic arthritis (JIA), having its onset before 16 years of age, varies between 3.8 and 400 per 100,000 [1, 3]. Considering the definition for an orphan disease in general as a condition affecting less than 7.5 people in 10,000 or less than 200,000 in the US or less than five in 10,000 in the European Union, orphan drug development is tremendously challenged by small sample sizes [2, 4, 5]. In addition, highly variable manifestations of rheumatologic diseases and onset in childhood complicate drug development. The US Orphan Drug Act was passed in 1983 to stimulate the investment into development of treatments for rare diseases by granting various incentives, such as 7 years’ marketing exclusivity, tax credit for 50 % of clinical trial costs, protocol assistance, Food and Drug Administration (FDA) fee waiver, and orphan grants...
programs [4]. The impact of the US orphan drug act on successful drug development for the treatment of rare rheumatologic diseases has not been systematically analyzed. We therefore analyzed how many orphan drugs were designated and subsequently approved by the FDA between 1983 and 2013 to treat rare rheumatologic diseases.

Methods

Search strategy

For quantitative analysis, we searched the publically available FDA database for orphan drug designations [6] using the following disease entities as search terms (terms for pediatric rheumatologic diseases in alphabetical order [7]): arthritis, antiphospholipid antibody syndrome, Behcet syndrome, collagenosis, CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly and telangiectasia), childhood and adolescence arthritis, CAPS (cryopyrin-associated periodic syndromes) such as CINCA/NOMID (chronic infantile neurologic cutaneous and articular syndrome/neonatal-onset multisystem inflammatory disease), MWS (Muckle-Wells syndrome) or FCAS (familial cold autoinflammatory syndrome), cutaneous leukocytoclastic vasculitis, dermatomyositis, diffuse sclerosis, drug induced lupus erythematosus, enthesitis-related arthritis, eosinophilic fasciitis (Shulman syndrome), eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), familial cold autoinflammatory syndrome, familial Mediterranean fever, Felty syndrome, granulomatosis with polyangiitis, Hyper IgD syndrome, idiopathic uveitis, IgA vasculitis (Henoch - Schönlein purpura), infantile sarcoidosis, isolated sacroiliitis, juvenile ankylosing spondylitis, juvenile idiopathic arthritis, Kawasaki syndrome, limited systemic scleroderma, localized scleroderma, lupus, microscopic polyangiitis, mixed connective tissue disease, non-bacterial osteitis, oligoarthritis, periodic fever syndromes, PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis, adenitis), polyarteritis nodosa, polymyositis, primary angitis of the central nervous system, psoriatic arthritis, relapsing polychondritis, rheumatoid factor negative polyarthritis, rheumatoid factor positive polyarthritis, Sharp syndrome, Sjögren's syndrome, spondyloarthritis due to chronic inflammatory intestinal disorders, spondyloarthritis due to psoriasis, spondylodiscitis, spondylololithesis, spondylolysis, systemic arthritis, systemic lupus erythematosus, systemic sclerosis, Takayasu arteritis, transient synovitis, TRAPS (tumor necrosis factor receptor associated periodic syndrome), undifferentiated juvenile idiopathic arthritis, and vasculitis (e.g., Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis). Non-English alphabet letters such as umlaut were searched with alternative spellings (e.g., ö was also entered as both o and oe). Acronyms were searched by both the acronym and the full wording. Disease terms with more than one word were searched with the full disease term and with each individual component of the term, e.g., “juvenile idiopathic arthritis” was searched as “juvenile”, “idiopathic”, “arthritis”, and “juvenile idiopathic arthritis”. All search results were subsequently checked for plausibility. All data entries from 1/1/1983 until 12/31/2013 were considered. Original terms from the FDA orphan drug database or FDA label were used to describe designated or approved indications to conform to source data.

Definitions

Identified compounds were categorized either according to their drug class or pharmacologic category. Within the respective classification, remaining compounds that could not be clearly allocated to a particular category were grouped as others. For classification according to their drug class, the compounds were accounted as small molecules or biologics. A small molecule was defined as a low-weight molecule (typically <1,000 Da) which is usually derived from chemical synthesis and can be fully characterized by analytical techniques [8, 9]. In contrast, biologics are large-molecular weight and structurally complex proteins that are derived from living cells through biotechnological processes (e.g., antibody methods, controlled gene expression or recombinant DNA) [8, 9]. Biologics were further differentiated into antibodies and fusion proteins. For classification according to pharmacologic category, compounds were grouped according to their mechanism of action which was gained from the FDA label for approved compounds. For the assessment of the putative mechanism of action of compounds that were not approved by the FDA, we started from the designated indication and selected the most likely mechanism of action causing the intended effect.

Statistics

Data were analyzed by standard methods of descriptive statistics with SAS Enterprise Guide version 5.1 (SAS, Cary, NC, USA). Continuous variables are presented as means, standard deviations, and ranges. For categorical variables, N and percentages were calculated. Time-to-approval was calculated as the time span from orphan drug designation to FDA approval.

Results

Orphan drug designations

Overall, 77 orphan drug designations were granted for 64 different compounds between 1983 and 2013 (Fig. 1, Table 1). The first orphan drug designations were granted in 1986 for two compounds, i.e. guanethidine monosulfate (for the treatment of moderate to severe reflex sympathetic dystrophy and causalgia) and dimethyl sulfoxide (for the treatment of cutaneous manifestations of scleroderma).
Both designations were subsequently withdrawn. Most designations per year were granted in 2011 ($N=8$). When analyzed according to drug classes, $33/77$ (43 %) designations were granted for 23 different biologics, $28/77$ (36 %) for 27 different small molecules and $14/77$ (18 %) designations for others representing 12 different compounds (Table 1). With two designations the drug class of the compounds was unknown (i.e., AI-RSA and Interleukin-1 Trap). Biologics were further differentiated into chimeric antibodies (4/33), human antibodies (10/33), humanized antibodies (8/33), unspecified antibodies (2/33) (i.e., human anti-tumor necrosis factor alpha monoclonal antibody and monoclonal antibody for immunization against lupus nephritis), fusion proteins (4/33), and other biologics (5/33) (i.e., anakinra, hanferon, interferon beta-1a, interleukin-1 receptor antagonist human recombinant, and a DNA plasmid pVGI.1 (VEGF2)) (Fig. 2).

**FDA approvals**
Between 1983 and 2013, $14/77$ (18 %) orphan drug designations received FDA approval representing 13 different compounds, because canakinumab was approved for two indications (Table 2, Fig. 1). Five drugs were approved for JIA, three for CAPS, three for uveitis, one for familial Mediterranean fever, one for ANCA associated vasculitis, and one for xerostomia and keratoconjunctivitis sicca in Sjögren’s syndrome patients (Table 2). The first approved orphan compound for a rare rheumatologic condition was pilocarpine hydrochloride for treating xerostomia and keratoconjunctivitis in Sjögren’s syndrome in 1998. Mean time (standard deviation) from designation to approval was 3.9 (2.81) [range 1 ... 12] years. Divided according to drug classes, $6/14$ (43 %) FDA orphan drug approvals comprised small molecules and $8/14$ (57 %) FDA orphan drug approvals were biologics. The time between orphan drug designation and time of approval was similar for biologics and small molecules (Fig. 3). Most pivotal trials were randomized controlled trials (Table 2).

**Withdrawn orphan drug designations**
Overall, $15/77$ (19 %) orphan drug designations (14 compounds) were withdrawn before approval (Table 3). The reasons for withdrawals were not captured in the FDA database.

**Pharmacologic categories of designated orphan drugs**
Designated compounds were immunomodulators, such as immunosuppressants, immunostimulants, tolerogens, or compounds with unspecified immunomodulatory properties, Nonsteroidal anti-inflammatory drugs (NSAIDs), expectorants, antibiotics, and angiogenic, antiarrhythmic, diagnostic, parasympathomimetic, and sympatholytic agents.

**Design of pivotal clinical trials and endpoints leading to FDA approval**
Only one pivotal trial, i.e. the study of anakinra for the treatment of neonatal onset inflammatory disease, was open label (Table 2). The other 12 approved compounds were studied for 13 indications in randomized controlled trials in which withdrawal designs were common. Colchicine received approval for the treatment of familial Mediterranean fever based on data available in the published literature. Most clinical trials were rather small and involved both children and adults. Studies were either uncontrolled (i.e., anakinra) or controlled with placebo (i.e., colchicine, rilonacept, canakinumab in both indications, etanercept, pilocarpine, adalimumab, and tocilizumab), sham procedure (i.e., dexamethasone intravitreal implant), before after control (i.e., fluocinolone acetonide intravitreal implant), or active control (i.e., meloxicam vs. naproxen, difluprednate ophthalmic solution vs. prednisolone, rituximab vs. cyclophosphamide in a non-inferiority design). Etanercept was studied as add-on therapy to an NSAID and/or prednisone.

**Discussion**
In 2013, 77 orphan drug designations for rare rheumatologic disorders were granted by the FDA whereof...
| Drug class               | Compound                                      | Designated indication according to FDA database                                                                 |
|-------------------------|-----------------------------------------------|---------------------------------------------------------------------------------------------------------------|
| Biologic                |                                               |                                                                                                               |
| Chimeric monoclonal antibody | Infliximab                                    | Treatment of juvenile rheumatoid arthritis. Treatment of giant cell arthritis. Treatment of chronic sarcoidosis. |
|                         | Rituximab                                     | For the use in combination with glucocorticoids for the treatment of patients with Wegener’s granulomatosis (WG) and microscopic polyangiitis (MPA). |
| Human monoclonal antibody | Adalimumab                                     | Treatment of juvenile rheumatoid arthritis.                                                                 |
|                         | Canakinumab                                    | Treatment of cryopyrin-associated periodic syndromes. Treatment of Tumor Necrosis Factor-receptor associated periodic syndrome (TRAPS). Treatment of hyperimmunoglobulinemia D and periodic fever syndrome. Treatment of familial mediterranean fever. |
|                         | Golimumumab                                    | Treatment of chronic sarcoidosis. Treatment of sarcoïdosis.                                                    |
|                         | Secukinumab                                    | Adjunctive treatment of chronic non-infectious uveitis requiring systemic immunosuppression.                   |
|                         | Ustekinumab                                    | Treatment of chronic sarcoidosis.                                                                             |
| Humanized monoclonal antibody | Eculizumab                                     | Treatment of dermatomyositis.                                                                               |
|                         | Gevokizumab                                    | Treatment of Behçet disease. Treatment of non-infectious intermediate, posterior or pan uveitis, or chronic non-infectious anterior uveitis. |
|                         | Humanized monoclonal antibody to CD40L (IDEC-131) | Treatment of systemic lupus erythematosus.                                                                    |
|                         | Humanized, afucosylated IgG1 kappa monoclonal antibody | Treatment of scleroderma.                                                                                   |
|                         | Mepolizumab                                    | Treatment of Churg-Strauss Syndrome.                                                                          |
|                         | Recombinant humanized monoclonal antibody 5c8  | Treatment of systemic lupus erythematosus.                                                                     |
|                         | Tocilizumab                                    | Treatment of pediatric patients (age 16 years and younger) with polyarticular-course juvenile idiopathic arthritis. |
| Unspecified monoclonal antibody | Human anti- Tumor Necrosis Factor alpha monoclonal antibody | Treatment of uveitis of the posterior segment of non-infectious etiology, and uveitis of the anterior segment of non-infectious etiology and refractory to conventional therapy. |
|                         | Monoclonal antibody for immunization against lupus nephritis | Treatment of lupus nephritis.                                                                                  |
| Fusion protein          | Etanercept                                     | Reduction in signs and symptoms of moderately to severely active polyarticular-course juvenile rheumatoid arthritis in patients who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs. Treatment of Wegener’s granulomatosis. |
|                         | Rilonacept                                     | Treatment of CIAS1-associated periodic syndromes. Treatment of familial Mediterranean fever.                  |
| Other                   | Anakinra                                       | Treatment of cryopyrin-associated periodic syndromes.                                                          |
|                         | Hanferon                                       | Treatment of Behçet disease.                                                                                   |
|                         | Interferon beta-1a                             | Treatment of juvenile rheumatoid arthritis.                                                                    |
|                         | Interleukin-1 receptor antagonist, human recombinant | Treatment of juvenile rheumatoid arthritis.                                                                   |
|                         | pVGI.1 (VEGF2)                                 | Treatment of thromboangiitis obliterans.                                                                        |
| Drug Class          | Indication                                                                                       |
|---------------------|--------------------------------------------------------------------------------------------------|
| Small molecule      | For use in conjunction with the UVAR photopheresis to treat diffuse systemic sclerosis.        |
| 8-methoxsalen       | Treatment of Behçet disease.                                                                     |
| Apremilast          | Treatment of lupus nephritis.                                                                    |
| Bindarit            | Treatment of mild to moderate keratoconjunctivitis sicca in patients with Sjögren’s syndrome.   |
| Bromhexine          | Treatment of lupus erythematosus (SLE) and the reduction in the use of steroids in steroid-dependent SLE patients. |
| Clindamycin hydrochloride | Treatment of sarcoidosis.                                                                        |
| Colchicine          | Treatment of familial Mediterranean fever.                                                      |
| Cyclosporine (ophthalmic) | Treatment of severe keratoconjunctivitis sicca associated with Sjogren’s syndrome.             |
| Dehydroepiandrosterone | Treatment of non-infectious ocular inflammation of the posterior segment in patients with intermediate, posterior, and panuveitis. |
| Dexamethasone (intravitreal implant) | Treatment of endogenous and traumatic anterior uveitis and panuveits.                        |
| Difluprednate (ophthalmic solution) | Treatment of juvenile rheumatoid arthritis.                                                      |
| Dimethyl sulfoxide  | Treatment of moderate to severe reflex sympathetic dystrophy and causalgia.                     |
| Flucinolone acetonide (intravitreal implant) | Treatment of severe keratoconjunctivitis sicca associated with Sjögren’s syndrome.          |
| Gammalinolenic acid | Treatment of Wegener’s granulomatosis.                                                           |
| Guanethidine monosulfate | Treatment of pediatric juvenile rheumatoid arthritis.                                        |
| Gusperimus trihydrochloride | Treatment of non-infectious posterior, intermediate and pan-uveitis.                         |
| Meloxicam           | Treatment of juvenile rheumatoid arthritis.                                                      |
| Methotrexate        | Treatment of juvenile rheumatoid arthritis.                                                      |
| Minocycline hydrochloride | Treatment of sarcoidosis.                                                                       |
| Nabumetone          | Treatment of severe keratoconjunctivitis sicca in patients with Sjögren’s syndrome.             |
| N-acetyl-procainamide | Prevention of life-threatening ventricular arrhythmias in patients with documented procainamide-induced lupus. |
| Nitric oxide        | Diagnosis of sarcoidosis.                                                                       |
| Pentoxifylline      | Treatment of Behçet disease.                                                                     |
| Pilocarpine HCl     | Treatment of xerostomia and keratoconjunctivitis sicca in Sjögren’s syndrome patients.          |
| Rofecoxib           | Treatment of juvenile rheumatoid arthritis.                                                      |
| Siponimod           | Treatment of polymyositis.                                                                      |
| Sirolimus           | Treatment of chronic/refractory anterior noninfectious uveitis, noninfectious intermediate uveitis, noninfectious panuveitis and non-infectious, uveitis affecting the posterior of the eye (NCUPS). |
| Thymopentin         | Treatment of lupus nephritis.                                                                    |
| Other               | Treatment of thromboangiitis obliterans (Buerger’s disease).                                    |
| Abetimus            | Treatment of chronic control of non-infectious posterior, intermediate and pan-uveitis.        |
| Allogeneic ex-vivo expanded placental adherent stromal cells | Treatment of thromboangiitis obliterans (Buerger’s disease).                                  |
| Bone marrow-derived mononuclear cells | Treatment of thromboangiitis obliterans (Buerger’s disease).                                |
| Cyclo [(E,Z)-(2S, 3R, 4R)-3-hydroxy-4-methyl-2-(methylamino)-nona-6,8-dienoyl]-L-2-aminobutyryl-N-methyl-glycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-valyl] | Treatment of chronic control of non-infectious posterior, intermediate and pan-uveitis. |
14 resulted in FDA approval comprising 13 different substances. Almost every fifth designation was withdrawn, mostly with unknown reasons. However, with etanercept safety reasons may have played a role in withdrawal: etanercept was studied in Wegener’s granulomatosis with a higher incidence of malignancies observed in the etanercept group compared with standard therapy [10, 11]. The success rate to achieve marketing approval in rheumatologic orphan drug development is comparable to overall success rates in orphan drug development, i.e. 14 % [12].

In general, failure of orphan drug applications are mainly attributed to the pivotal clinical trial design (e.g. choice of endpoints and target population), inexperience in orphan drug development of sponsors, and a low level of interaction with the FDA (e.g. protocol assistance) [13]. These factors seem to be interdependent because inexperienced sponsors may choose inadequate pivotal clinical trial designs and may benefit most from FDA protocol assistance. The reasons why compounds were withdrawn or not approved e.g. lack of efficacy, safety issues or due to commercially driven decisions, are not available in the FDA database. Although, this information would be of

| Drug Class and Indications | Continued |
|----------------------------|-----------|
| Human gammaglobulin         | Treatment for juvenile rheumatoid arthritis. |
|                            | Treatment of idiopathic inflammatory myopathies. |
| Immune globulin intravenous (IVG) | Treatment of juvenile rheumatoid arthritis. |
|                            | Treatment of polymyositis/dermatomyositis. |
| Kre-Celazine (Oral Buffered Creatine-Cetylated Fatty Acid Compound) | Treatment of juvenile rheumatoid arthritis joint and related tissue inflammation in the pediatric population. |
| Lactobacillus brevis CD2     | Treatment Behçet disease. |
| L-pyr-L-glu-L-gln-L-leu-L-glu-L-arg-L-alal-L-leu-L-ser-L-ser | Treatment of neuropathic pain in patients with sarcoidosis. |
| Natural human lymphoblastoid interferon-alpha | Treatment of Behçet disease. |
| Peptide 144 (TGF beta-1-inhibitor) | Treatment of localized scleroderma. |
| Purified type II collagen    | Treatment of juvenile rheumatoid arthritis. |
| Unknown                     | AI-RSA |
| Interleukin-1 Trap           | Treatment of autoimmune uveitis. |

| Technology platform |
|---------------------|
| Biologic antibody   |
| Biologic antibody humanised |
| Biologic, antibody chimera |
| Biologic fusion protein |
| Biologic, other     |
| Small molecule      |
| Other               |
| Unknown             |

Fig. 2 Orphan drugs for rare rheumatologic disorders: year of orphan drug designation by technology platform
Table 2 Orphan drugs for the treatment of rare rheumatologic disorders approved by the FDA between 1983 and 2013

| Compound                        | Approved indication according to FDA label                                                                 | Pharmacologic category | Designation year | Approval year | Pivotal clinical trial | Reference |
|---------------------------------|-------------------------------------------------------------------------------------------------------------|------------------------|------------------|---------------|------------------------|-----------|
| Pilocarpine hydrochloride       | Treatment of dry mouth in patients with Sjögren’s syndrome                                                | Cholinergic agonist    | 1992             | 1998          | RCT 256 mean 57 years (24 – 85) 12 weeks Global improvement of dry mouth | [26]      |
| Etanercept                      | Reduction in signs and symptoms of moderately to severely active polyarticular-course juvenile rheumatoid arthritis in patients who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs | Tumor necrosis factor-alpha inhibitor | 1998             | 1999          | RCT 69 2 – 17 years 7 months JIA definition of improvement criteria | [10]      |
| Dexamethasone (intravitreal implant) | Treatment of non-infectious uveitis affecting the posterior segment of the eye                           | Glucocorticoid         | 1998             | 2010          | RCT 153 n/a 8 weeks Vitreous haze score and 3-line improvement from baseline in best corrected visual acuity | [27]      |
| Fluocinolone acetonide (intravitreal implant) | Treatment of chronic non-infectious uveitis affecting the posterior segment of the eye                       | Glucocorticoid         | 2000             | 2005          | RCT 108 n/a 3 years Rate of recurrence of uveitis affecting the posterior segment of the study eye | [28]      |
| Meloxicam                       | For relief of the signs and symptoms of pauciarticular or polyarticular course juvenile rheumatoid arthritis in patients 2 years of age or older | NSAID                  | 2002             | 2005          | RCT n/a ≥2 years 12 weeks ACR Pediatric 30 | [29]      |
| Rilonacept                      | Treatment of cryopyrin-associated periodic syndromes                                                      | Interleukin inhibitor  | 2004             | 2008          | RCT 47 n/a 24 weeks CAPS symptom score | [30]      |
| Adalimumab                      | Treatment of juvenile idiopathic arthritis                                                                  | Tumor necrosis factor-alpha inhibitor | 2005             | 2008          | RCT 171 4 – 17 years 32 weeks ACR Pediatric 30 | [31]      |
| Rituximab                       | For the use in combination with glucocorticoids for the treatment of patients with Wegener’s granulomatosis and microscopic polyangiitis | Selective immunosuppressant | 2006             | 2011          | RCT 197 ≥15 years 18 months Birmingham Vasculitis Activity Score for Granulomatosis with Polyangiitis | [16]      |
| Colchicine                      | Treatment of familial Mediterranean fever                                                                 | Mitotic poison         | 2007             | 2009          | Evidence for the efficacy was derived from the published literature. | [32]      |
| Drug               | Indication                                                                 | Type               | FDA Approval Year | Disease Duration | Study Duration | Measure of Response | Additional Assessments                                      | Notes |
|--------------------|----------------------------------------------------------------------------|--------------------|-------------------|------------------|-----------------|--------------------|-------------------------------------------------------------|-------|
| Canakinumab        | Treatment of cryopyrin-associated periodic syndromes, in adults and children 4 years of age and older | Interleukin inhibitor | 2007              | 9 – 74 years     | 8 weeks         | Minimal or better for physician’s assessment of disease activity, assessment of skin disease, and serum levels of C-Reactive Protein and Serum Amyloid A | [19]  |
| Canakinumab        | Treatment of active systemic juvenile idiopathic arthritis in patients aged 2 through 16 years | Interleukin inhibitor | 2008              | 4 – 74 years     | 4 weeks         | Adapted ACR Pediatric 30 and absence of fever | [19]  |
| Difluprednate      | Treatment of endogenous anterior uveitis                                   | Glucocorticoid     | 2008              | n/a              | 2 weeks         | Difference in anterior chamber cell grade                | [33]  |
| Anakinra           | Treatment of neonatal-onset multisystem inflammatory disease               | Interleukin inhibitor | 2010              | 0.7 – 46 years   | 60 months       | Disease-specific Diary Symptom Sum Score               | [34]  |
| Tocilizumab        | Treatment of active polyarticular juvenile idiopathic arthritis in patients 2 through 16 years of age | Interleukin inhibitor | 2012              | 2 – 17 years     | 24 weeks        | JIA ACR 30 flare                                        | [20]  |

ACR Pediatric 30: American College of Rheumatology Pediatric 30 response, CAPS: Cryopyrin-associated periodic syndromes, JIA: Juvenile Idiopathic arthritis, JIA ACR 30 flare: Juvenile idiopathic arthritis American College of Rheumatology 30 flare, JRA: Juvenile rheumatoid arthritis, n/a: not applicable or no information is provided in the FDA label, NSAID: Nonsteroidal anti-inflammatory drugs, OL: Open label, RCT: Randomized controlled trial, uncontrolled, SJIA: Systemic juvenile idiopathic arthritis.
value for the clinician as it may protect patients from unnecessary exposure to further research and should be made publically available.

By definition, drug development in orphan diseases is challenged by small sample sizes [5]. In addition, disease-specific factors, such as the prevalence, disease class, and scientific output, influence success rates in orphan drug development [14]. Rheumatologic diseases include complex pathomechanisms which complicates identification of potential drug targets. Most of the designated compounds target autoimmune and subsequent inflammatory reactions. Particularly, immunomodulators play a pivotal role in disease modification by modulating various pathophysiologically relevant targets in the inflammatory process e.g., antibodies against specific surface antigens on lymphocytes, glucocorticoids that inhibit transcription of inflammatory cytokines such as interleukins and TNF-alpha, decoy receptors, or antagonists for receptors of inflammatory proteins. In addition, compounds that relieve symptoms associated with rheumatologic diseases were designated as orphan drugs, such as pilocarpine-HCl which increases lacrimal secretion and hence alleviates xerostomia and keratoconjunctivitis sicca in Sjögren’s syndrome patients. Nitric oxide (NO), a biomarker of airway inflammation, received orphan drug designation for the diagnosis of sarcoidosis. However, the diagnostic clinical trial could not detect a difference in exhaled NO levels between patients and controls [15]. All remaining 76 orphan drug designations for rheumatologic conditions were of therapeutic purpose.

Orphan drugs for rheumatologic disease hold indications in other disease areas by targeting pathways also relevant in other conditions. For example, rituximab, which is a selective immunosuppressant targeting CD20 surface proteins on B-lymphocytes, is also approved for treatment of Non-Hodgkin’s Lymphoma and Chronic Lymphocytic Leukemia [16]. In contrast, orphan drugs for lysosomal storage disorders target a specific pathway that is unique for the respective conditions. For instance, although Fabry
disease and Gaucher disease are sphingolipidoses, the therapeutic enzyme for Fabry disease (agalsidase alfa or beta) is different to the enzyme replacement therapy in Gaucher disease (recombinant glucocerebrosidase) [17, 18].

The choice for or against an orphan drug development pathway can vary within same disease entity: both tocilizumab and canakinumab are approved for the treatment of systemic juvenile idiopathic arthritis. Of interest, the orphan program with canakinumab consisted of two studies with \( N = 261 \) participants followed for 4 and 48 weeks, whereas the non-orphan tocilizumab program had only one clinical trial and involved \( N = 112 \) subjects with a study duration of 12 weeks [19, 20]. Sample size and design of pivotal clinical trials for the approved rheumatologic orphan drug indication varied. Most studies were randomized placebo controlled trials which corroborates that drug development in rare diseases is possible at a high level of evidence. The FDA guidance for industry for the development of drug products for the treatment of rheumatoid arthritis recommends the use of efficacy endpoints capturing clinical remission and prevention of structural damage, suggests to limit the use of placebo both in short-term and long-term trials, and encourages study designs with active comparators [21]. Endpoints in clinical trials of the orphan drugs approved for rheumatologic disorders included categorical variables such as number of attacks in familial Mediterranean fever under colchicine, rate of recurrence of uveitis under fluocinolone acetonid intravitreal implant, disease scores such as vitreous haze score or anterior chamber cell grade for uveitis under difluprednate ophthalmic emulsion or dexamethasone intravitreal implant, multisystem composite disease scores, such as the Birmingham Vasculitis Activity Score for Granulomatosis with Polyangiitis [22] or the American College of Rheumatology Pediatric 30 criteria for improvement which comprises subjective, objective and biochemical components [23]. For the future, it would be desirable to capture the impact of the tested intervention on patients’ needs by including patient centered outcome measures such as the Canadian Occupational Performance Measure as clinical trial endpoints where possible [24]. As signals may not become evident or may not be detectable in the initial small and short clinical trials (Table 2), it is desirable to follow-up on the long-term effectiveness and safety outcome in systematic disease registries after drug approval. Compared to oncological orphan drugs with a shorter time to approval, orphan drug designations in rheumatologic diseases seem to be either set earlier in the drug development process or the process from designation to approval may be slower [12]. In general, orphan drug designations are granted during the final steps of the drug development process [25]. Although, the orphan drug designation is arbitrary in the drug development process, time to approval allows an approximate estimation of orphan drug approvals of currently filed designated orphan drugs.

This quantitative analysis has several limitations. We made the assumption that the designation of a compound

| Withdrawn compound | Designation year | Designated indication according to FDA database |
|--------------------|-----------------|-----------------------------------------------|
| Dimethyl sulfoxide  | 1986            | Cutaneous manifestations of scleroderma       |
| Guanethidine monosulfate | 1986 | Moderate to severe reflex sympathetic dystrophy and causalgia |
| Bromhexine         | 1989            | Mild to moderate keratoconjunctivitis sicca in patients with Sjögren’s syndrome |
| Immune globulin intravenous (human) | 1992 | Juvenile rheumatoid arthritis |
| Immune globulin intravenous (human) | 1992 | Polymyositis/dermatomyositis |
| AI-RSA             | 1992            | Autoimmune uveitis                           |
| Methotrexate       | 1993            | Juvenile rheumatoid arthritis                |
| Dehydroepiandrosterone | 1994 | Systemic lupus erythematosus (SLE) and the reduction in the use of steroids in steroid-dependent SLE patients |
| Interferon beta-1a | 1998            | Juvenile rheumatoid arthritis                |
| Humanized MAb (IDEC-131) to CD40L | 1999 | Systemic lupus erythematosus |
| Etanercept         | 1999            | Wegener’s granulomatosis                      |
| pVGL.1 (VEGF2)     | 1999            | Thromboangiitis obliterans                    |
| Infliximab         | 2003            | Giant cell arteritis                          |
| Human Anti-tumor Necrosis factor alpha monoclonal antibody | 2003 | Uveitis of the posterior segment of non-infectious etiology, and uveitis of the anterior segment of non-infectious etiology and refractory to conventional therapy |
| Golimumab          | 2004            | Chronic sarcoidosis                          |
as an orphan drug was considered a surrogate for the intent to develop a drug for a disease. However, not all manufacturers may seek orphan drug designation by the FDA and information may therefore not be transparent, e.g. due to patent considerations. The amount of designations might be prone to bias since one compound might be designated as an orphan drug several times, e.g. interleukin 1-trap and rilonacept. The true duration of the development program may not be reflected by time to approval because the time of orphan designation may be arbitrary in the drug development process and, thus does not allowing a comparison between orphan drug development and non-orphan drug development. Data from the European Medicine Agency data were not formally analyzed. We chose this approach, because the European orphan legislation was only introduced in 2000. Therefore, the European database is less comprehensive compared to the one hosted by the FDA. However, drug development for orphan conditions is a global effort. EMA orphan drug designations show similar trends (data not shown). Therefore, the present formal analysis of the FDA data and their impact for patients around the world are considered generalizable.

Conclusions

In conclusion, orphan drug development is challenging: 30 years of US orphan drug act delivered 14 orphan drug programs with anti-rheumatic or supportive compounds for six rare rheumatologic conditions. Although, rarity and diversity of conditions account for the small sizes all but one pivotal study were randomized controlled trials.

Abbreviations

- ANCA: anti-neutrophil cytoplasmic antibody; CAPS: cryopyrin-associated periodic syndrome; CINCA: chronic infantile neurologic cutaneous and articular syndrome; CREST syndrome: calcinosis, Raynaud’s phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia; DNA: deoxyribonucleic acid; FCAS: familial cold autoinflammatory syndrome; FDA: Food and Drug Administration; IgA: immunoglobulin A; IgD: immunoglobulin D; JIA: juvenile idiopathic arthritis; MWS: Muckle–Wells Syndrome; NO: nitric oxide; NOMID: neonatal-onset multisystem inflammatory disease; NSAID: nonsteroidal anti-inflammatory drug; PFAPA syndrome: periodic fever, aphthous stomatitis, pharyngitis, adenitis; TRAPS: tumor necrosis factor receptor associated periodic syndrome; VEGF2: vascular endothelial growth factor

Competing interests

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Authors’ contributions

TL has contributed to the acquisition, analysis, and interpretation of the data, critical revision of the manuscript for important intellectual content, and material support. AL has contributed to the acquisition, analysis, and interpretation of the data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and statistical analysis. GHF contributed to the interpretation of the data, critical revision of the manuscript for important intellectual content, and manuscript support. MR has conceptualized the design of the study, contributed to the acquisition, analysis, and interpretation of the data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and statistical analysis. All authors approved the final version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors confirm that they had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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