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Supplementary information

Juvenile idiopathic arthritis

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Supplementary table 1:

List of approved conventional synthetic (cs-) and biologic (b-) disease-modifying anti-rheumatic drugs (b-DMARDs) approved for the care of JIA by the European Medicine Agency (EMA) or the Food and Drug Administration (FDA).

Drug (route)	Type	Target	Indication	Route and Dose	Refs
Conventional synthetic DMARDs					
Methotrexate	Synthetic	Folic acid antagonist	Polyarticular JIA ≥3 years	oral, sc: 10-20 mg/m²/(BSA)/week	[1]
Biologic DMARDs					
Abatacept	Human	CD80/86 CTL4Ig	Polyarticular JIA ≥6 years (iv) ≥2 years (sc)	**iv:** 10 mg/kg week (max 1 gr) 0, 2, 4, then q4 weeks **sc:** 10 to <25 kg 50 mg/week, 25 to <50 kg 87.5 mg/week, ≥50 kg 125 mg/week	[2]
Adalimumab	Human	TNF-α	Polyarticular JIA ≥2 years Enthesitis-related arthritis (ERA) ≥6 years Chronic non-infectious anterior uveitis≥2 years	**sc:** 10-30 kg 20 mg/ every other week ≥ 30 kg 40 mg/every other week	[3]
Anakinra	Human	IL-1	Systemic JIA ≥8 months or older at least 10 kg in NSAIDS or glucocorticoids failures	**sc:** >50 kg 100 mg/day < 50 kg 1-2 mg/kg/day	4, 5
Canakinumab	Human	IL-1	Systemic JIA ≥2 years in NSAIDS and glucocorticoids failures	**sc:** ≥7,5 kg: 4 mg/kg/dose/every 4 weeks (max 300 mg)	[6-8]
Etanercept	Human	TNF-R	Polyarthritis (rheumatoid RF±) and extended oligoarthritis ≥2 years psoriatic arthritis and enthesitis related arthritis≥12 years	**sc:** 0.4 mg/kg/twice weekly (max 25 mg) 0.8 mg/kg/weekly (max 50 mg)	[7-9]
Golimumab	Human		Polyarticular JIA ≥2 years	**sc:** <40 kg 30 mg/m²/(BSA)/monthly (max 40 mg) ≥40 kg 50 mg/monthly	[10]
Tocilizumab	Humanized	IL-6	sJIA≥2 years for iv and ≥1 year for sc in NSAIDS and glucocorticoids failures	**iv:** <30 kg 12 mg/kg/every 2 weeks ≥30 kg 8 mg/kg/ every 2 weeks **sc:** 10-30 kg 162 mg/every 2 weeks ≥30 kg 162 mg/every week	[11, 12]
Tocilizumab	Humanized	IL-6	Polyarticular JIA≥2 years	**iv:** <30 kg 8 mg/kg/ every 4 weeks ≥30 kg 10 mg/kg/ every 4 weeks **sc:** 10-30 kg 162 mg/every 3 weeks ≥30 kg 162 mg/every 2 week	[13, 14]
Small molecules					
Tofacitinib	**synthetic**	JAK inhibitor	Polyarticular JIA and PsA≥2 years	**Oral,** 10- <20 kg: 3.2 mg (3.2 mL)/twice a day 20- <40 kg: 4 mg (4mL)/twice a day ≥40 kg: 5 mg (5mL)/twice a day	[15, 16]

sc: subcutaneous; iv: intravenous; IL: interleukin; eow: every other week

Supplementary table 2:

Panel A. PRINTO not-profit international collaborative research projects (40,559 children from 196 centres in 51 countries) [52]

The not-for-profit studies have been the results of willingness by the paediatric rheumatology community to collaborate on a wide international base for common research and clinical objectives.

PRINTO Not-for-profit studies	Patients	Ref
MTX high dose trial (2004)	633	[1]
CHAQ CHQ JIA patients (2001)	3,235	[17]
CHAQ CHQ Healthy children (2001)	3,409	[17]
JSLE core set of outcome (2006)	557	[18-22]
JDM core set of outcome (2008)	295	[18, 23-27]
Cyclosporine A trial JIA (2006)	344	[28]
Antares JIA (2008)	213	[29]
Childhood Vasculitides (2010)	1,399	[30, 31]
MTX Withdrawal trial JIA (2010)	364	[32]
JDM Trial (2017)	138	[33, 34]
EPOCA JIA (2019)	1,3814	[35, 36]
PHARMACHILD JIA (2018)*	9,068	[37, 38]
EUROFEVER (autoinflammatory diseases) (2010)*	4,551	[39-42]
ABIRISK JIA Registry (2015)	155	[43]
MAS classification criteria JIA (2016)	1,111	[44-50]
INSAID registry (other)*	26	-
PRINTO JIA classification*	1,199	[51]
The STARS JIA trial*	70	-
DAISY JIA*	26	-
HyperPED-COVID (other)*	235	-
Total number of children	**40,842**	**-**

MTX: methotrexate, CHAQ: Childhood Health Assessment Questionnaire (CHAQ); CHQ: Child Health Questionnaire (CHQ); JSLE: juvenile systemic lupus erythematosus; JDM: juvenile Dermatomyositis; JIA: juvenile idiopathic arthritis; MAS: macrophage activation syndrome; *study ongoing;

Panel B. PRINTO/PRCSG phase II/III for-profit clinical trials in collaboration with pharmaceutical companies (4331 children from 268 centres in 40 countries). Updated information on PRINTO projects are available on the PRINTO website

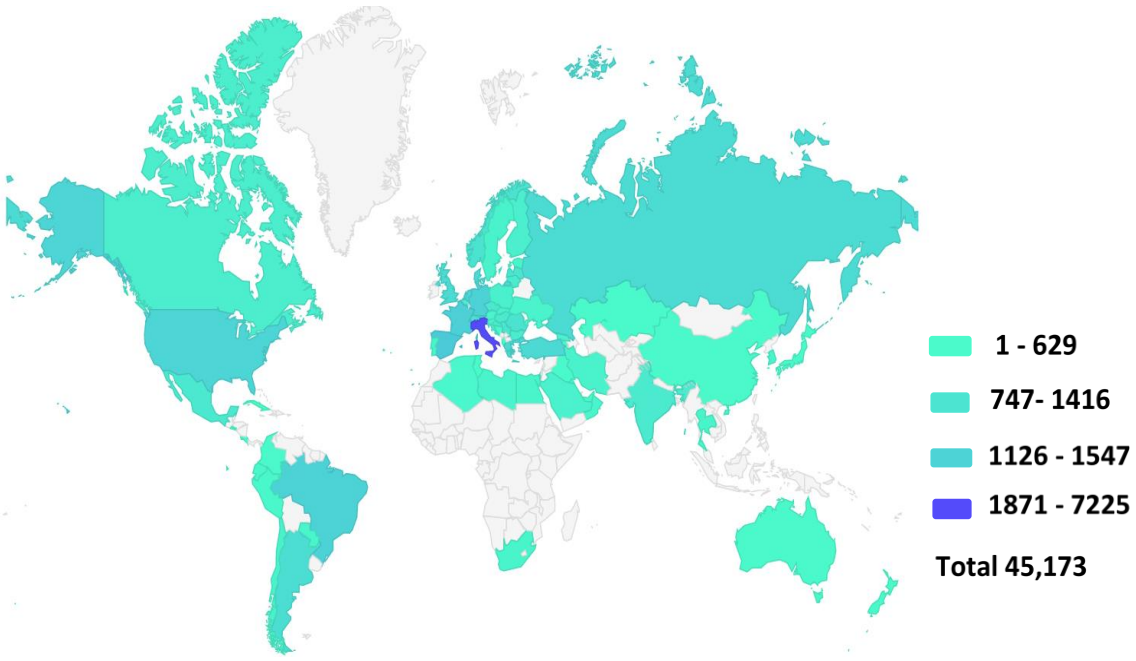
The collaborative work for profit trials led to the successful implementation of the so-called paediatric legislation (see main text) as witnessed by the European Medicines Agency (EMA) who state "The last 10 years have seen some considerable progress in the availability of medicines for children in certain therapeutic fields because of the Regulation. Rheumatology or infectious diseases are often referred to as prime examples. The significant surge of new treatments for children with rheumatologic diseases following the completion of PIPs has transformed a sector, which was previously neglected".

PRINTO/PRCSG for profit clinical trials	**Patients**	**Ref**
Etanercept sc (2000)	69	[9]
Meloxicam oral (2005)	225	[17]
Systemic JIA registry (2006)	327	-
Infliximab iv (2007)	122	[17, 53]
Adalimumab sc (2008)	171	[3, 19-22, 54]
Abatacept iv (2008)	190	[2]
Tocilizumab sJIA iv (2012)	112	[11, 12]
Canakinumab phase II sc (2012)	26	[6]
Canakinumab phase III sc (2012)	190	[55, 56]
Etanercept sc (2014)	127	[7, 8]
Tocilizumab poly iv (2015)	188	[13, 14]
Tofacitinib phase II oral (2017)	17	[15]
Golimumab sc (2018)	173	[10]
Abatacept sc (2018)	219	[57]
Adalimumab registry sc (2020)	849	[58]
Abatacept registry iv-sc (2020)	499	-
Belimumab iv jSLE (2020)	93	[59]
Golimumab iv (2021)	127	[60]
Tocilizumab sc (2021)	103	[61]
Tofacitinib phase III poly oral (2020)	225	[16]
Certolizumab pegol sc (NCT01550003)*	193	-
Secukinumab sc (NCT03031782)*	86	-
Total number of children	**4,331**	**-**

*study ongoing; sc: subcutaneous, iv intravenous

Supplementary figure 1:

Geographic representation of the not-for-profit PRINTO international projects[52] and PRINTO/PRCSG for-profit clinical trials in collaboration with pharmaceutical companies.



PRINTO not-for-profit enrolments 1996-2021 (N=40,842)
PRINTO/PRCSG for profit clinical trials enrolments 2000-2021 (N=4,331)

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