Clin Pharmacokinet (2015) 54:35–80
DOI 10.1007/s40262-014-0208-4

REVIEW ARTICLE

Pharmacokinetics and Pharmacokinetic–Pharmacodynamic Relationships of Monoclonal Antibodies in Children

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Published online: 17 December 2014

Abstract Monoclonal antibodies (mAbs) constitute a therapeutically and economically important drug class with increasing use in both adult and paediatric patients. The rather complex pharmacokinetic and pharmacodynamic properties of mAbs have been extensively reviewed in adults. In children, however, limited information is currently available. This paper aims to comprehensively review published pharmacokinetic and pharmacokinetic–pharmacodynamic studies of mAbs in children. The current status of mAbs in the USA and in Europe is outlined, including a critical discussion of the dosing strategies of approved mAbs. The pharmacokinetic properties of mAbs in children are exhaustively summarised along with comparisons to reports in adults: for each pharmacokinetic process, we discuss the general principles and mechanisms of the pharmacokinetic/pharmacodynamic characteristics of mAbs, as well as key growth and maturational processes in children that might impact these characteristics. Throughout this review, considerable knowledge gaps are identified, especially regarding children-specific properties that influence pharmacokinetics, pharmacodynamics and immunogenicity. Furthermore, the large heterogeneity in the presentation of pharmacokinetic/pharmacodynamic data limited clinical inferences in many aspects of paediatric mAb therapy. Overall, further studies are needed to fully understand the impact of body size and maturational changes on drug exposure and response. To maximise future knowledge gain, we propose a 'Guideline for Best Practice' on how to report pharmacokinetic and pharmacokinetic–pharmacodynamic results from mAb studies in children which also facilitates comparisons. Finally, we advocate the use of more sophisticated modelling strategies (population analysis, physiology-based approaches) to appropriately characterise pharmacokinetic–pharmacodynamic relationships of mAbs and, thus, allow for a more rational use of mAb in the paediatric population.

Key Points

Careful review of the current knowledge of the pharmacokinetic and pharmacokinetic–pharmacodynamic characteristics of monoclonal antibodies (mAbs) in children has identified a considerable knowledge gap, especially with respect to mechanistic insight regarding the impact of physiological and developmental aspects.

We provide a 'Guideline for Best Practice' on how to report study results in order to gain maximum knowledge and enable comparison, e.g. across studies, across the mAb drug class, and with adult characteristics.

More sophisticated modelling approaches (population analysis, physiology based) are needed to appropriately characterise the complex pharmacokinetics/pharmacodynamics of mAbs in children, preferably also considering body size and maturation processes.

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1 Introduction

Therapeutic monoclonal antibodies (mAbs) have gained large attention over recent decades given their desirable features, such as high potency and limited off-target toxicity. mAbs now constitute a therapeutically and economically important drug class, evident by the growing number of mAbs on the market and in development [1]. An increased use of mAbs has also been seen in the paediatric population, especially in the areas of inflammatory diseases, organ transplantation and oncology [2].

mAbs are large proteins with a structure similar to endogenous immunoglobulins. They comprise two domains: (i) the variable antigen-binding region (Fab), responsible for the specificity to the target antigen; and (ii) the constant region (Fc), triggering immune responses through interaction with Fc receptors (FcR) [3]. Immunoglobulins are grouped into five classes according to their structure: IgA, IgD, IgE, IgG and IgM. IgG is the predominant type representing approximately 80 % of endogenous immunoglobulins in serum, and the only subtype currently represented in mAbs. mAbs are also commonly classified based on their genetic origin: murine, chimeric, humanised or fully human; all of which are in therapeutic use. More details about the structure of mAbs and the different types can be found in Dirks and Meibohm [3] and Keizer et al. [4].

The pharmacokinetics and pharmacodynamics of mAbs are often complex and *mutually* influenced, i.e. molecules bind to their target with high affinity and to a significant extent, such that the interaction may have an impact on the pharmacokinetics of the drug [5]. These processes have been extensively reviewed in adults [3, 4, 6–9] but the information available in children is limited. Paediatric patients represent a special population: as children grow and develop, body size and composition change alongside with maturation processes. These changes may modify absorption, distribution, elimination and response to the drug [10–12].

This paper aims to critically review available pharmacokinetic and pharmacokinetic–pharmacodynamic characteristics of mAbs in children. For this purpose, mAbs (approved and in development) have been identified utilising multiple sources: the online drug databases of the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) [13, 14], as well as paediatric investigation plans (PIPs) and post-marketing Pediatric Research Equity Acts (PREAs) from the two agencies, respectively. Thereafter, an exhaustive literature search of pharmacokinetic and pharmacokinetic–pharmacodynamic studies was undertaken: a PubMed search was performed using the international non-proprietary names (INNs) of the mAbs or 'monoclonal antibody(ies)' combined with keywords such as 'pharmacokinetic*', 'pharmacodynamic*', 'concentrations of …', 'neonate(s)', 'infant(s)', 'child(ren)', 'paediatric/pediatric' and/or 'adolescent(s)'. In addition, Google Scholar was used to identify cited abstracts or publications not indexed in PubMed. Studies were included regardless of the legal status of the mAb, i.e. approved, in development, off-label use or withdrawn from the market; mAb fragments were not included.

The first sections of this review concentrate on the mAbs in the paediatric population in the USA and Europe. To round-off, immunogenicity is discussed with respect to its impact on paediatric mAb therapy. Throughout the review, future perspectives in the clinical use and development of mAbs in paediatric patients are highlighted.

2 Current Status of Monoclonal Antibodies in the Paediatric Population

2.1 Approved mAbs

At present (April 2014), approximately one-third of all mAbs approved for adults in the European and/or US market are also approved for paediatric use. In addition, one mAb (palivizumab) has been approved solely for paediatric use given its therapeutic indication. In total, 11 mAbs are licensed for use in the paediatric population (nine in the USA and eight in Europe) [13, 14]. No murine mAb is currently marketed for paediatric use, probably due to increasing interest in humanised and fully human mAbs. The approved paediatric indication(s), their age ranges and dosing regimens can be found in Table 1.

Palivizumab is approved for the youngest children, starting at 35 weeks of gestational age, followed by daclizumab which is approved for children ≥11 months. The majority of the mAbs are, however, approved for older children. The indication and age range are frequently the same in Europe and the USA but in a few cases (e.g. adalimumab) one, or both, aspect(s) differ. For these mAbs it can be observed that for the same indication they are approved for younger children by the EMA than by the FDA.

Oral administration is not feasible for mAbs in general. Hence, they are administered intravenously ($n = 6$), subcutaneously ($n = 4$) or intramuscularly ($n = 1$). The route of administration in the paediatric population corresponds to that in adults, except for tocilizumab being only

Table 1 Monoclonal antibodies approved by the European Medicines Agency and/or the US Food and Drug Administration for use in paediatric populations

INN (trade name)	Antibody type	Target(s)	Approved paediatric indication(s)[a,b]	Approved age range(s)[a,b]	Administration route	Approved dosing regimen
Adalimumab (Humira®)	Human	TNF-α	Crohn's disease[b]	≥6 years[b]	SC injection	<40 kg: 40 mg at week 0, thereafter 20 mg q2w ≥40 kg: 80 mg at week 0, thereafter 40 mg q2w
			Polyarticular juvenile idiopathic arthritis[a,b]	≥4 years[a]; ≥2 years[b]	SC injection	24 mg/m^2 BSA q2w (2–4 years: max. 20 mg; 4–12 years: max. 40 mg) ≥13 years: 40 mg q2w
Basiliximab (Simulect®)	Chimeric	IL-2Rα (=CD25)	Prophylaxis of acute organ rejection[b]	≥1 year[b]	IV bolus or short infusion	<35 kg: 10 mg at day 0 and day 4 ≥35 kg: 20 mg at day 0 and day 4
Canakinumab (Ilaris®)	Human	IL-1β	Cryopyrin-associated periodic syndromes[a,b]	≥4 years[a]; ≥2 years and ≥7.5 kg[b]	SC injection	≥7.5 to <15 kg: 4 mg/kg q8w ≥15 to <40 kg: 2 mg/kg q8w ≥40 kg: 150 mg q8w
			Systemic juvenile idiopathic arthritis[a,b]	≥2 years[a,b]	SC injection	≥7.5 kg: 4 mg/kg q4w (max. 300 mg)
Daclizumab (Zenapax®)	Humanised	IL-2Rα (=CD25)	Prophylaxis of acute kidney rejection[a]	≥11 months[a]	IV infusion	1.0 mg/kg q2w (5 doses in total)
Denosumab (Xgeva®)	Human	RANKL (=TNFSF11)	Giant cell tumour of bone[a]	Skeletally mature adolescents[a]	SC injection	120 mg q4w + 120 mg at days 8 and 15 of first month
Eculizumab[c] (Soliris®)	Humanised	C5	Atypical haemolytic uraemic syndrome[b]	Not specified, dose by BW from 5 kg[b]	IV infusion	5 to <10 kg: 300 mg q1w at weeks 1–2, thereafter 300 mg q3w 10 to <20 kg: 600 mg at week 1, 300 mg at week 2, thereafter 300 mg q2w 20 to <30 kg: 600 mg q1w at weeks 1–3, thereafter 600 mg q2w 30 to <40 kg: 600 mg q1w at weeks 1–2, 900 mg at week 3, thereafter 900 mg q2w ≥40 kg: 900 mg q1w weeks 1–4, 1,200 mg at week 5, thereafter 1,200 mg q2w
			Paroxysmal nocturnal haemoglobinuria[b]	Not specified, dose by BW from 5 kg[b]	IV infusion	5 to <10 kg: 300 mg q1w at weeks 1–2, thereafter 300 mg q3w 10 to <20 kg: 600 mg at week 1, 300 mg at week 2, thereafter 300 mg q2w 20 to <30 kg: 600 mg q1w at weeks 1–3, thereafter 600 mg q2w 30 to <40 kg: 600 mg q1w at weeks 1–2, 900 mg at week 3, thereafter 900 mg q2w ≥40 kg: 600 mg q1w at weeks 1–4, 900 mg at week 5, thereafter 900 mg q2w
Infliximab (Remicade)	Chimeric	TNF-α	Crohn's disease[a,b]	≥6 years[a,b]	IV infusion	5 mg/kg at 0, 2 and 6 weeks, thereafter q8w
			Ulcerative colitis[a,b]	≥6 years[a,b]	IV infusion	5 mg/kg at 0, 2 and 6 weeks, thereafter q8w
Omalizumab (Xolair®)	Humanised	IgE Fc	IgE-mediated (allergic) asthma[a,b]	≥12 years[a]; ≥6 years[b]	SC injection	Dosing schedule according to BW and baseline IgE concentrations (max. 600 mg q2w)
			Chronic spontaneous/ ideopathic urticaria[a,b]	≥12 years[a,b]	SC injection	150 or 300 mg q4w[a] 300 mg q4w[b] (note: dose independent of IgE or BW)
Palivizumab (Synagis®)	Humanised	RSV glycoprotein F	RSV infections[a,b]	35 weeks gestational age to <2 years[a,b]	Intramuscular injection	15 mg/kg q4w during anticipated RSV risk
Raxibacumab (Raxibacumab)	Human	Anthrax protective antigen	Anthrax inhalation[a]	Not specified, dose by BW[a]	IV infusion	<15 kg: 80 mg/kg ≥15 to <50 kg: 60 mg/kg ≥50 kg: 40 mg/kg

Table 1 continued

INN (trade name)	Antibody type	Target(s)	Approved paediatric indication(s)[a,b]	Approved age range(s)[a,b]	Administration route	Approved dosing regimen
Tocilizumab (Actemra®[a], RoActemra®[b])	Humanised	IL-6R	Polyarticular juvenile idiopathic arthritis[a,b]	≥2 years[a,b]	IV infusion[d]	<30 kg: 10 mg/kg q4w ≥30 kg: 8 mg/kg q4w
			Systemic juvenile idiopathic arthritis[a,b]	≥2 years[a,b]	IV infusion[d]	<30 kg: 12 mg/kg q2w ≥30 kg: 8 mg/kg q2w

BSA body surface area, *BW* body weight, *C5* complement component 5, *EMA* European Medicines Agency, *Fc* constant domain of immunoglobulins, *FDA* US Food and Drug Administration, *IgE* immunoglobulin E, *IL* interleukin, *IL-xR* IL-*x* receptor, *INN* international non-proprietary name, *IV* intravenous, *max.* maximum, *qxw* every *x* weeks, *RANKL* receptor activator of nuclear factor-κB ligand, *RSV* respiratory syncytial virus, *SC* subcutaneous, *TNF-α* tumour necrosis factor- α

[a] FDA approval

[b] EMA approval

[c] Orphan approval EMA

[d] SC injection or IV infusion for adults

available for intravenous administration in children (no explanation available on the label).

2.2 Off-Label Use

Off-label use constitutes a common practice in paediatric patients [15, 16] and the mAb drug class is no exception. An increased off-label use of mAb therapies has been observed for a wide variety of indications, mostly as second-line treatment [2]. Rituximab, as one example of a widely used mAb without any approved indication in the paediatric population, has been administered in a spectrum of diseases including haematological and renal disorders [17–19]. There are also many examples of mAbs with one or several approved paediatric indication(s) being used for other indications [20–23]. Although these reports in general point towards beneficial effects, they should be interpreted carefully as most of them only include small numbers of patients and lack control groups [18]. Additionally, the dosing strategies vary considerably between the studies, e.g. a body size-normalised adult dose [24] or identical to an approved paediatric indication. As is discussed in the sections below, these approaches might be particularly precarious when dealing with mAbs, since pharmacokinetic/pharmacodynamic aspects may differ between adults and children [12] as well as between indications.

2.3 mAbs in Development

Safety and efficacy studies in the paediatric population are more challenging than in adults, not only due to physiological differences and changes during childhood, but also from ethical and practical considerations [25]. Consequently, fewer studies are in general carried out in this group. In recent years, however, requirements to conduct clinical trials in children have increased. All European applications for new marketing authorisation now have to include a PIP describing study results covering all paediatric age groups and necessary age-appropriate formulations [26], although a waiver may be granted, e.g. if the indication is irrelevant for the paediatric population. The FDA has so far established PREAs but will soon introduce the Pediatric Study Plan (PSP) [27], an equivalent to the PIP.

Currently, 38 mAbs are registered with a (non-waived) PIP and/or PREA (Table 2). Some have already been approved in adults ($n = 14$) and are aiming to extend the age range, while others are still in clinical development ($n = 24$). Although some studies plan to include infants or neonates, the majority are planned for children ≥2 years. Thus, the to date limited pharmacokinetic and pharmacokinetic–pharmacodynamic information in children is certainly about to increase.

Table 2 Monoclonal antibodies with a Paediatric Investigation Plan or a post-marketing Pediatric Research Equity Act

INN (trade name)	Antibody type	Target(s)	Potential paediatric indication(s)	Planned age range(s)	Clinical trials planned to finish
Adalimumab (Humira®)	Human	TNF-α	Hidradenitis suppurativa	≥12 years[b]	Dec 2015[b]
			Chronic plaque psoriasis	≥4 years[a,b]	May 2014[b]
			Ulcerative colitis	≥5 years[b]	Jun 2019[b]
Alemtuzumab (Lemtrada®)	Humanised	CD52	Multiple sclerosis	≥10 years[b]	Sep 2018[b]
Alirocumab	Human	PCSK9	Hypercholesterolaemia	≥8–10 years[b]	Sep 2023[b]
Belimumab (Benlysta®)	Human	BAFF (=TNFSF13B)	Systemic lupus erythematosus	≥5 years[a,b]	Mar 2016[b]
Benralizumab	Humanised	IL-5Rα (=CD125)	Eosinophilic persistent asthma	≥5 years[b]	Apr 2029[b]
Bevacizumab (Avastin®)	Humanised	VEGF-A	High-grade glioma	≥6 months[b]	Sep 2016[b]
			Non-rhabdomyosarcoma soft tissue sarcoma	≥6 months[b]	Sep 2016[b]
			Rhabdomyosarcoma	Not specified[a]; ≥6 months[b]	Sep 2016[b]
Brentuximab vedotin (Adcetris®)	Chimeric	CD30 (=TNFRSF8)	Anaplastic large cell lymphoma	≥2 years[b]	Dec 2018[b]
			Hodgkin's lymphoma	≥5 years[b]	Dec 2018[b]
Briakinumab	Human	IL-12 and IL-23	Psoriasis vulgaris	≥6 years[b]	Dec 2019[b]
cαStx1 and cαStx2	Chimeric	Shiga toxin 1 and 2	Shiga toxin-mediated complications	From birth[b]	Dec 2015[b]
Denosumab (Xgeva®, Prolia®)	Human	RANKL (=TNFSF11)	Glucocorticoid-induced osteoporosis, osteogenesis imperfect	≥2 years[b]	Dec 2022[b]
			Giant cell tumour of bone[d]	≥12 years[b]	Dec 2014[b]
Eculizumab (Soliris®)	Humanised	C5	Shiga-toxin-producing *Escherichia coli* haemolytic uraemic syndrome	From birth[b]	Jun 2019[b]
Epratuzumab	Humanised	CD22	Systemic lupus erythematosus	≥5 years[b]	Mar 2021[b]
Etrolizumab/ rhuMAb β7	Humanised	β7 subunit of integrins α4β7 and αEβ7	Ulcerative colitis	≥4 years[b]	Jan 2024[b]
Evolocumab/AMG 145	Human	PCSK9	Familial hypercholesterolaemia	≥12 years[b]	Jul 2017[b]
Golimumab (Simponi®)	Human	TNF-α	Polyarticular juvenile idiopathic arthritis	≥2 years[a]; ≥3 years[b]	Aug 2014[b]
			Ulcerative colitis	≥4 years[b]	Sep 2021[b]
Ipilimumab (Yervoy®)	Human	CTLA-4 (=CD152)	Melanoma	≥12 years[b]	Jun 2018[b]
			Solid malignant tumours	From birth[b]	Jun 2015[b]
Ixekizumab	Humanised	IL-17A	Systemic juvenile idiopathic arthritis	≥1 years[b]	Oct 2025[b]
			Other types of juvenile idiopathic arthritis	≥2 years[b]	Oct 2025[b]
			Psoriasis vulgaris	≥6 years[b]	Oct 2025[b]
Lebrikizumab	Humanised	IL-13	Asthma	≥6 years[b]	Jan 2024[b]
Mepolizumab	Humanised	IL-5	Asthma	≥6 years[b]	Oct 2017[b]
			Hypereosinophilic syndrome, eosinophilic oesophagitis	From birth[b]	Jun 2020[b]
Motavizumab	Humanised	RSV glycoprotein F	Serious lower respiratory tract disease caused RSV in children at high risk of RSV disease (prophylaxis)	From birth to <2 years[b]	Mar 2009[b]
Natalizumab (Tysabri®)	Humanised	Integrin α4	Crohn's disease	≥6 years[a]	Jun 2017[a]
			Multiple sclerosis	≥10 years[b]	Sep 2015[b]
NSC764038	Chimeric	Ganglioside G2	Neuroblastoma	≥28 days[b]	Jan 2014[b]
Obinutuzumab (Gazyva®)	Humanised	CD20	B cell lymphoma, Burkitt and Burkitt-like lymphoma/ leukaemia	≥6 months[b]	Jun 2024[b]
Ocrelizumab	Humanised	CD20	Multiple sclerosis	≥10 years[b]	Mar 2021[b]
Olokizumab	Humanised	IL-6	Juvenile idiopathic arthritis	≥1 years[b]	Jun 2023[b]
Pagibaximab	Chimeric	Staphylococcal lipoteichoic acid	Prevention of bacterial sepsis	Preterm newborns; 0.50 to ≤1.2 kg[b]	Jan 2014[b]
Quilizumab	Humanised	IGHE	Allergic asthma	≥6 years[b]	Feb 2025[b]
Rituximab (MabThera®[b], Rituxan®[a])	Chimeric	CD20	B cell malignancies	≥6 months[b]	Jun 2019[b]
			Wegener's granulomatosis and microscopic polyangiitis	≥2 years[b]	May 2016[b]
Sarilumab	Human	IL-6Rα	Juvenile idiopathic arthritis	≥1 years[b]	Jun 2022[b]
Secukinumab	Human	IL-17A	Juvenile idiopathic arthritis	≥2 years[b]	Dec 2018[b]

Table 2 continued

INN (trade name)	Antibody type	Target(s)	Potential paediatric indication(s)	Planned age range(s)	Clinical trials planned to finish
Sirukumab/ CNTO136	Human	IL-6	Juvenile idiopathic arthritis	≥1 years[b]	Jun 2023[b]
Tabalumab/ LY2127399	Human	BAFF/(=TNFSF13B)	Systemic lupus erythematosus	≥5 years[b]	Mar 2021[b]
Teplizumab/ MGA031[c]	Humanised	CD3	Type 1 diabetes mellitus	≥2 years[b]	Dec 2018[b]
Tocilizumab (Actemra®[a], RoActemra®[b])	Humanised	IL-6R	Juvenile idiopathic arthritis	≥1 years[a]	Oct 2015[b]
Tralokinumab	Human	IL-13	Asthma	≥6 years[b]	Jun 2024[b]
Ustekinumab (Stelara®)	Human	IL-12 and IL-23	Juvenile idiopathic arthritis	≥6 years[b]	Mar 2024[b]
			Chronic plaque psoriasis	≥6 years[a,b]	Dec 2021[b]
Vedolizumab	Humanised	Integrin α4β7	Crohn's disease	≥4 years[b]	Sep 2021[b]
			Ulcerative colitis	≥4 years[b]	Sep 2021[b]

INNs in bold indicate no approved indication at present (April 2014), non-bold INNs are mAbs with at least one approved indication in adults and/or children

BAFF B cell activating factor, *C5* complement component 5, *CD*x cluster of differentiation *x*, *CTLA-4* cytotoxic T lymphocyte-associated protein 4, *EMA* European Medicines Agency, *Fc* constant domain of immunoglobulins, *FDA* US Food and Drug Administration, *IGHE* immunoglobulin heavy constant E, *IL* interleukin, *IL-xR* interleukin-*x* receptor, *INN* international non-proprietary name, *mAbs* monoclonal antibodies, *PCSK9* proprotein convertase subtilisin/kexin type 9, *RANKL* receptor activator of nuclear factor-κB ligand, *RSV* respiratory syncytial virus, *TNF-α* tumour necrosis factor-α, *VEGF-A* vascular endothelial growth factor A

[a] Post-marketing Pediatric Research Equity Act (by the FDA)

[b] Paediatric investigation plan (by the EMA)

[c] mAb with modified Fc-region

[d] Indication already approved by the FDA

3 Dosing Strategies of Approved mAbs

Dose selection strategies for mAbs approved for children include (i) a fixed dose for the approved age range; (ii) fixed doses for different body weight (BW) intervals; and (iii) linear dose scaling by body surface area (BSA, i.e. mg/m^2) or by BW (i.e. mg/kg). There are a few examples that combine the two last strategies, e.g. tocilizumab, which is dosed 10 mg/kg to patients <30 kg and 8 mg/kg to patients ≥30 kg [28]. Very little information is available regarding the rationale behind the chosen posology. If the dosing regimen in adults was based on BW or BSA (i.e. mg/kg or mg/m^2), the same regimen was commonly used in children. Otherwise, dose reduction based on BW or BSA was performed; whether a pharmacokinetic and/or pharmacodynamic scaling approach was applied beforehand or not was only mentioned for raxibacumab (mAb against anthrax). Raxibacumab has not been tested in children (due to ethical reasons) and the approval is based solely on adult data [14]. However, no further information regarding the used (covariate) model was provided.

In a paediatric population BW considerably varies, suggesting that dose adjustment according to body size may be a reasonable approach. The strategy of simply adjusting dose or pharmacokinetic parameters linearly according to BW or BSA is, however, frequently questioned [29–31] (see [29, 32] for details on scaling principles). The linear BW model under-predicts drug clearance (CL) while the BSA model over-predicts CL in children when compared with allometric scaling [31]. In addition, several equations for calculation of BSA exist [33–35]; equations developed only on adults [35] should be applied carefully given the anatomical differences compared with children. Moreover, relevant maturation processes that might affect the pharmacokinetics of mAbs may not be directly related to body size, as is the case for small molecules (e.g. hepatic enzymes or kidney function). Further discussion on these aspects is provided in Sect. 4. Dosing regimens linearly based on BW or BSA may also have drawbacks from a convenience perspective in terms of drug preparation, drug administration and risk of medication errors [30]. As long as information technology (IT)-related solutions are not available to guide dose selection in daily clinical practice, a fixed dosing regimen for a given BW range may represent a more pragmatic alternative. Furthermore, it is important to remember that when adjusting dosing regimens based on these scaling principles, the effective and safe plasma concentration range is assumed to be the same across ages, which might not always be the case. Since mAbs possess unique pharmacokinetic–pharmacodynamic characteristics, a good understanding of the physiological differences between adults and children, affecting not only pharmacokinetic but also pharmacodynamic processes, as well as the relationship between the two (in both populations), is needed to achieve optimal dosing paradigms.

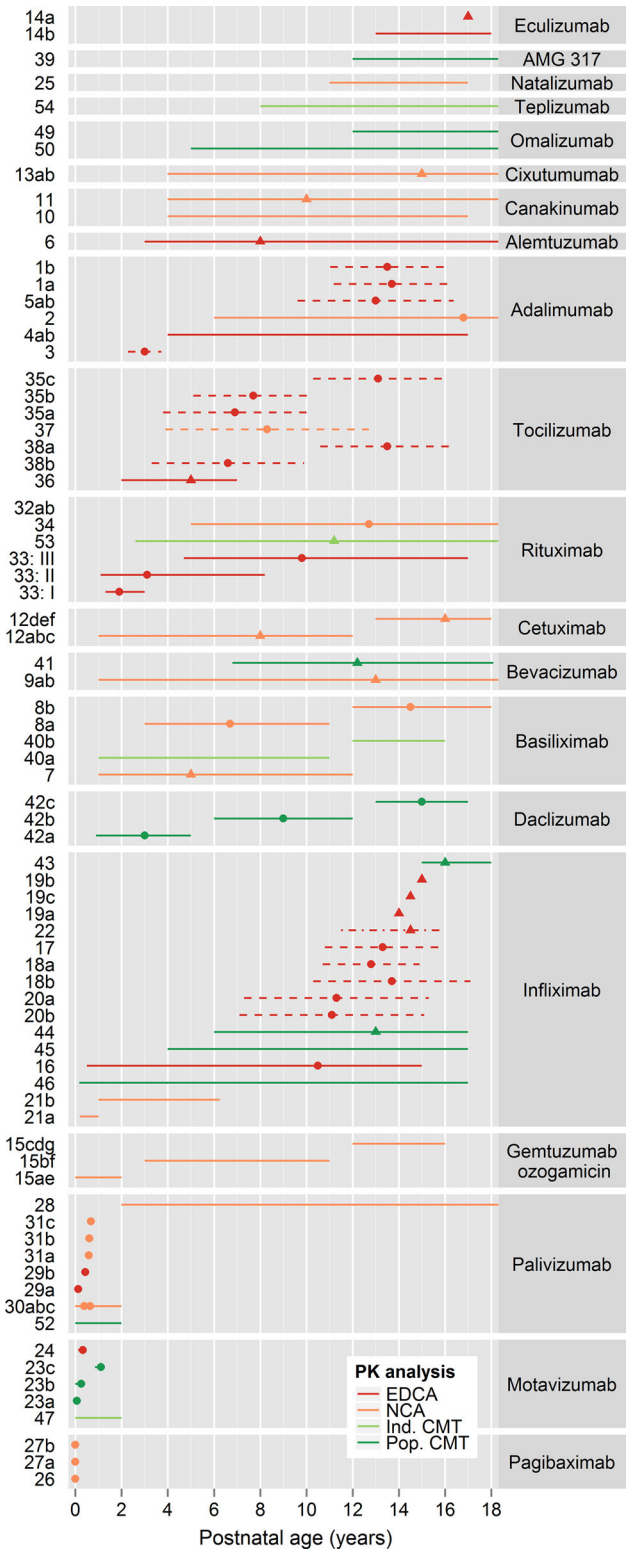

Fig. 1 Post-natal age of paediatric patients included in the pharmacokinetic studies or, if applicable, the respective subpopulations, as reported. The numbers on the *y*-axis refer to the number assigned in the 'Study no.' column of Tables 3 and 5. The *colours* indicate the type of pharmacokinetic analysis performed, *points* indicate the mean, *dashed lines* indicate ±1 standard deviation from the mean, *triangles* indicate the median, *solid lines* indicate the range and *dot-dashed lines* indicate the interquartile range. *EDCA* exploratory drug concentration analysis, *Ind. CMT* individual compartmental analysis, *NCA* non-compartmental analyses, *PK* pharmacokinetic, *Pop. CMT* population compartmental analysis

4 Pharmacokinetics

The pharmacokinetic characteristics of mAbs in adults have been extensively reviewed [4, 6–8, 36]; however, little has been accomplished in the paediatric arena [37]. In the subsequent sections, the characteristics of the different pharmacokinetic processes (absorption, distribution, elimination) are summarised and critically discussed. Each subsection starts with a brief summary of the general principles and mechanisms, followed by a discussion of the biological aspects in children that influence the pharmacokinetic processes. Furthermore, the pharmacokinetic parameters in children are comprehensively summarised and compared with reports in adults. For this purpose, a thorough literature search was undertaken (see Sect. 1), identifying a total number of 54 studies (understood as different pharmacokinetic analyses) covering the full paediatric age range from pre-term to 18 years (Fig. 1). For most of the mAbs, a large gap in the information in pharmacokinetic understanding was observed for neonates and infants, consistent with the observations of the approved age ranges of the mAbs.

Overall, the level of complexity varied among the reviewed data analyses. More than two-thirds of the studies only reported (i) distributions of measured drug concentrations at a certain point in time (37 %)—these studies will hereafter be referred to as 'exploratory drug concentration analysis' (EDCA); or (ii) non-compartmental analysis (NCA) (33 %). A considerably smaller proportion of studies performed compartmental analysis, either at an individual (Ind. CMT) or population (Pop. CMT) level (8 or 22 %, respectively). The type of reported pharmacokinetic parameters naturally differed depending on the type of performed analysis. For that reason, the results have been summarised in two sets of tables. For EDCA and NCA, the key characteristics of the studies with respect to dosing regimen, age and BW ranges, indication and type of pharmacokinetic analysis are outlined in Table 3 and the extracted pharmacokinetic parameters in Table 4. Although the area under the plasma concentration–time curve (*AUC*), the maximum concentration (C_{max}) and minimum concentration (C_{min}) will not be explicitly compared across studies due to their dose-dependent nature, they have been included in Table 4 to provide information about ranges of observed drug concentrations/exposure. Information available only in plots has been digitalised (using WebPlotDigitizer: http://arohatgi.info/WebPlotDigitizer/app/) and included in Table 4. Likewise,

Table 3 Key features of pharmacokinetic studies (exploratory drug concentration analysis or non-compartmental analysis) of monoclonal antibodies in children, regardless of the their legal status (i.e. approved, in development, off-label use or withdrawn; hence, Table 3 includes monoclonal antibodies additional to those in Tables 1 and 2)

Study no.	Indication	Study information for PK evaluation	PK analysis	No. of individuals	Age (years)[a]	BW (kg)[b]	Dose	Dosing regimen (administration route[c])	ADA$^+$ (%)	Refs.
Adalimumab										
1a	Crohn's disease	2 dose levels evaluated	EDCA	93	13.7; 2.52	46.3; 16.79	160 mg, 80 mg, then: <40 kg: 20 mg ≥40 kg: 40 mg	160 mg at week 0, 80 mg at week 2, thereafter q2w (SC). Dosing regimen intensified to q1w for patients exhibiting disease flares	2.3	[13, 89]
1b				95	13.5; 2.47	44.4; 13.96	80 mg, 40 mg, then: <40 kg: 10 mg ≥40 kg: 20 mg	80 mg at week 0, 40 mg at week 2, thereafter q2w (SC). Dosing regimen intensified to q1w for patients exhibiting disease flares	4.4	
2	Focal segmental glomerulosclerosis	PK after single dose and at steady state	NCA	$n_{paed} = 7$ $n_{adult} = 3$	16.8; 9.0 (6–36)[d]	BSA: 2.2; 1.0 m^2	24 mg/m^2	q2w, 9 doses in total (SC)	n.r.	[90]
3	Polyarticular juvenile idiopathic arthritis		EDCA	15	3; 0.72[e]	13.4; 2.0[e]	24 mg/m^2 (max. 20 mg)	q2w (SC)	6.7	[13, 91]
4a	Polyarticular juvenile idiopathic arthritis	2 dose levels evaluated. Data from open-label fixed-dose phase of total study	EDCA	171	11.1–11.7[f] (eligible: 4–17)	40.9–45.4[f]	<30 kg: 20 mg	q2w (SC)	6[g], 26[h]	[14, 87]
4b							≥30 kg: 40 mg	q2w (SC)		
5a	Polyarticular juvenile idiopathic arthritis	2 dose levels evaluated. Dose escalation from 20 to 40 mg allowed ($n = 3$)	EDCA	8	13.0; 3.38[e]	39.5; 12.3[e]	<30 kg: 20 mg	q2w (SC)	Week 24: 16 [15[g], 20[h]]	[88]
5b				17			≥30 kg: 40 mg	q2w (SC)	Week 60: 24 [15[g], 60[h]]	
Alemtuzumab										
6	Acute lymphoblastic leukaemia		EDCA	4	8 (3–20)[e]	n.r.	See regimen	Start at 0.06 mg/kg, escalating to 0.6 mg/kg over following 4 days. 9 doses of 0.6 mg/kg over following 3 weeks (2 h IV infusion)	"None"	[77]
Basiliximab										
7	Prevention of acute renal transplant rejection		NCA	6	5 (1–12)	16.7; 6.3 (10.4–28.0)[d]	10 mg	Day 0 and 4 (20–30 min IV infusion)	n.r.	[66]
8a	Prevention of acute renal transplant rejection	Parameters reported for 2 age groups comparing with or without MMF. Ind. CMT analysis also performed but parameters n.r.	NCA	16	6.7; 3.3 (3–11)[d]	22.9; 9.3	<35 kg: 10 mg ≥35 kg: 20 mg	Day 0 and 4 (IV bolus)	n.r.	[65]
8b				27	14.5; 1.7 (12–18)[d]	46.6; 8.9	<35 kg: 10 mg ≥35 kg: 20 mg	Day 0 and 4 (IV bolus)		
Bevacizumab										
9a	Solid tumours	2 dose levels evaluated. PK evaluated after first dose	NCA	3	13 (1–21)[e]	n.r.	5 mg/kg	Day 1 and 15 (30–90 min IV infusion)	n.r.	[92]
9b				5			15 mg/kg	Day 1 and 15 (30–90 min IV infusion)		
Canakinumab										
10	Cryopyrin-associated periodic syndrome	CL, V_d, AUC, and $t_{½}$ only evaluated in 3 of the patients	NCA	5	4–17[i]	31.2; 13.3 (17.2–52)[d]	<40 kg: 2 mg/kg ≥40 kg: 150 mg	≥1 dose(s), re-treatment at relapse allowed ($n = 6$) (SC)	"None"	[78, 79]

Table 3 continued

Study no.	Indication	Study information for PK evaluation	PK analysis	No. of individuals	Age (years)[a]	BW (kg)[b]	Dose	Dosing regimen (administration route[c])	ADA$^+$ (%)	Refs.
11	Systemic juvenile idiopathic arthritis	C_{max} and t_{max} only evaluated in 6 of the patients	NCA	21	10 (4–19)	>12 (eligible)	0.5, 1.5 or 4.5 mg/kg	Single dose, second dose on day 3 or 8 if needed (SC)	"None"	[80, 81]
Cetuximab										
12a	Advanced refractory solid tumours	3 dose levels evaluated. Each dose level divided into 2 age groups	NCA	7	8 (1–12)	n.r.	75 mg/m^2	Cycle: od days 1–5 and 8–12, repeated every 21 days (1 h IV infusion)	4	[93]
12b				7			150 mg/m^2			
12c				9			250 mg/m^2			
12d				4	16 (13–18)		75 mg/m^2			
12e				2			150 mg/m^2			
12f				6			250 mg/m^2			
Cixutumumab										
13a	Refractory solid tumours	Phase I and II studies using 2 dose levels. C_{max} after 9 mg/kg evaluated in 14 patients, C_{min} in 17 patients/dose group	NCA	7	15 (4–28)[e]	n.r.	6 mg/kg	q4w (1 h IV infusion)	n.r.	[94]
13b				9			9 mg/kg	q4w (1 h IV infusion)		
Eculizumab										
14a	Atypical haemolytic uraemic syndrome	2 trials reported: trial 1 (14a) and trial 2 (14b). Both report parameters from induction and maintenance phase of therapy	EDCA	1	17	n.r.	See regimen	Induction: 900 mg q1w for 4 weeks, 1,200 mg at week 5, thereafter maintenance: 1,200 mg q2w (IV)	n.r.	[95]
14b				5	13–18[i]	n.r.	See regimen	Induction: 900 mg q1w for 4 weeks, 1,200 mg at week 5, thereafter maintenance: 1,200 mg q2w (IV)		
Gemtuzumab ozogamicin										
15a	Refractory or relapsed acute myeloid leukaemia	Conjugated antibody. 3 dose levels evaluated. Dose selected based on BSA except for children <3 years, who received corresponding doses based on BW	NCA	3	0–2[i]	n.r.	0.2 mg/kg	2 doses separated by 14–28 days (2 h IV infusion)	n.r.	[96]
15b				4	3–11[i]	n.r.	6 mg/m^2	2 doses separated by 14–28 days (2 h IV infusion)		
15c				7	12–16[i]	n.r.	6 mg/m^2	2 doses separated by 14–28 days (2 h IV infusion)		
15d				2	14.6; 2.1 (13–16)[d]	n.r.	7.5 mg/m^2	2 doses separated by 14–28 days (2 h IV infusion)		
15e				2	0–2[i]	n.r.	0.3 mg/kg	2 doses separated by 14–28 days (2 h IV infusion)		
15f				5	3–11[i]	n.r.	9 mg/m^2	2 doses separated by 14–28 days (2 h IV infusion)		
15g				7	12–16[i]	n.r.	9 mg/m^2	2 doses separated by 14–28 days (2 h IV infusion)		
Infliximab										
16	Crohn's disease		EDCA	28	10.5; 3.3 (0.5–15)[d]	n.r.	5 mg/kg	Single dose or 3 infusions at weeks 0, 2 and 6. Retreatment allowed at relapse: on-demand ($n = 20$) or scheduled 5/10 mg/kg q8w ($n = 3$). Switch from on-demand to scheduled ($n = 11$) (3 h IV infusion)	35.7	[97]

Table 3 continued

Study no.	Indication	Study information for PK evaluation	PK analysis	No. of individuals	Age (years)[a]	BW (kg)[b]	Dose	Dosing regimen (administration route[c])	ADA$^+$ (%)	Refs.
17	Crohn's disease	2 dose levels evaluated: q8w or q12w. PKs for q8w group ($n = 51$) summarised in Adedokun et al. [98]	EDCA	112	13.3; 2.5	43.8; 14.6	5 mg/kg	Weeks 0, 2 and 6, thereafter q8w or q12w (IV infusion)	2.9	[98, 99]
18a	Crohn's disease	Open-label extension of Hyams et al. [99]. 3 dose levels evaluated, concentrations reported for 2 of them	EDCA	14	12.8; 2.1	43.4; 18.8[e]	5 mg/kg	Weeks 0, 2 and 6, thereafter q8w (IV infusion)	4.8	[100]
18b				7	13.7; 3.4	45.8; 15.8[e]	10 mg/kg	Weeks 0, 2 and 6, thereafter q8w (IV infusion)	4.8	
19a	Crohn's disease	3 dose levels evaluated. Age-stratified: <13/13–17 years	EDCA	6	14[j]	47.1[k]	1 mg/kg	Single dose (2 h IV infusion)	Week 12: "none"	[82, 83]
19b				7	15[j]	45.1[k]	5 mg/kg	Single dose (2 h IV infusion)	Week 12: "none"	
19c				8	14.5[j]	54.8[k]	10 mg/kg	Single dose (2 h IV infusion)	Week 12: "none"	
20a	Polyarticular juvenile rheumatoid arthritis	2 dose levels evaluated. All received concomitant methotrexate	EDCA	60	11.3; 4.0	n.r.	3 mg/kg	Weeks 0, 2 and 6, thereafter q8w (40–120 min IV infusion)	38	[101]
20b				62	11.1; 4.0	n.r.	6 mg/kg	Weeks 0, 2 and 6, thereafter q8w (40–120 min IV infusion)	12	
21a	Kawasaki disease	Parameters reported for 2 age groups	NCA	6	2.4–12 months[i]	n.r.	5 mg/kg	Single dose (IV)	16.7	[23]
21b				10	12–75 months[i]	n.r.	5 mg/kg	Single dose (IV)	20	
22	Ulcerative colitis	2 dose levels (q8w, q12w) but parameters reported together. Groups stratified by baseline corticosteroid use	EDCA	60	14.5 (11.5–16.0)[m]	50.8 (36.6–59.4)[m]	5 mg/kg	Weeks 0, 2 and 6, thereafter q8w or q12w (IV infusion)	7.7	[13, 98]
Motavizumab										
23a[n]	Prophylaxis of RSV infection	2 phases of the study: phase I = dose-escalation phase; phase II = randomized phase. 2 dose levels reported	Pop. CMT[n]	I: 6	0.73; 0.21 months	4.15; 2.12	3 mg/kg	Every 30 days, 1–5 doses in total (IM)	"None"	[84]
23b[n]				I: 211	3.02; 3.61 months		15 mg/kg	Every 30 days, 1–5 doses in total (IM)	3.3	
23c[n]				II: 66	13.3; 3.1 months		15 mg/kg	Every 30 days, 1–5 doses in total (IM)		
24	Prophylaxis of RSV infection		EDCA	93	3.9; 2.4 months	4.7; 1.7	15 mg/kg	Every 30 days, 5 doses in total (IM)	5	[102]
Natalizumab										
25	Crohn's disease	PK evaluated after first and third dose	NCA	38	11–17[i]	n.r.	3 mg/kg	q4w, 3 doses in total (IV infusion)	8	[103, 104]
Pagibaximab										
26	Prevention of *Staphylococcal* sepsis	Dose escalation study, PK data given as means across all dose groups	NCA	33	27.6 weeks gest. age[k]	1.00; 0.167	10, 30, 60 or 90 mg/kg	q2w, 2 doses in total (IV infusion)	"None"	[63]

Table 3 continued

Study no.	Indication	Study information for PK evaluation	PK analysis	No. of individuals	Age (years)[a]	BW (kg)[b]	Dose	Dosing regimen (administration route[c])	ADA$^+$ (%)	Refs.
27a	Prevention of *Staphylococcal* sepsis	2 dose levels reported	NCA	20	27.4; 1.79 weeks gest. age	0.981; 0.194	60 mg/kg	q1w, 3 doses in total (IV infusion)	"None"	[85]
27b				22	27.5; 1.60 weeks gest. age	1.00; 0.152	90 mg/kg	q1w, 3 doses in total (IV infusion)	"None"	
Palivizumab										
28	Treatment of active RSV infection in patients with haematopoietic stem cell transplant	2 studies reported, 1 including paediatric patients	NCA	15	36[k] (eligible: 2–60, not separate for paediatrics)	n.r.	15 mg/kg	Single dose (IV infusion)	"None"	[86]
29a	RSV infection	Dose escalation study. Parameters reported for 2 dose levels	EDCA	8	1.5; 0.4 months	3.96; 0.35	5 mg/kg	Single dose (IV infusion, rate: 10–20 mg/min)	n.r.	[105]
29b				22	5.2; 0.9 months	6.75; 0.46	15 mg/kg	Single dose (IV infusion, rate: 10–20 mg/min)		
30a	Prophylaxis of RSV infection	Dose escalation study, 3 dose levels evaluated. PKs reported for 5 and 15 mg/kg	NCA	11	4.6–7.6[f] (premature <24) months[i]	n.r.	5 mg/kg	q4w, 2–5 doses in total (IM)	15	[106]
30b				3	4.6–7.6[f] (premature <24) months[i]	n.r.	10 mg/kg	q4w, 2–5 doses in total (IM)		
30c				48	4.6–7.6[f] (premature <24) months[i]	n.r.	15 mg/kg	q4w, 2–5 doses in total (IM)		
31a	Prophylaxis of RSV infection	Dose escalation study, 3 dose levels evaluated	NCA	10	6.9; 1.28 months	4.89; 5.41[e]	3 mg/kg	Every 27–37 days, max. 5 doses (2–5 min IV infusion)	5	[107]
31b				10	7.3; 2.01 months		10 mg/kg	Every 27–37 days, max. 5 doses (2–5 min IV infusion)		
31c				22	8.1; 1.69 months		15 mg/kg	Every 27–37 days, max. 5 doses (2–5 min IV infusion)		
Rituximab										
32a	B cell non-Hodgkin's lymphoma	2 groups: patients divided into intermediate-risk (32a) and high-risk groups (32b). $t_{½}$ estimated only for those with ≥3 measurements after the last dose	EDCA	26	<30 (eligible)	n.r.	375 mg/m^2	4 cycles in total: first and second: day −2 and 0; third and fourth: day 0. A substudy was run starting rituximab only on the second cycle (IV infusion, gradually increased infusion rate)	n.r.	[108]
32b				15	<30 (eligible)	n.r.	375 mg/m^2			
33	Opsoclonus-myoclonus syndrome	3 groups (I, II, III) based on concomitant medication. Concentrations of rituximab, however, summarised together	EDCA	I: 12 II: 8 III: 5	I: 1.9; 0.52 (1.3–3)[d] II: 3.1; 2.3 (1.1–8.2)[d] III: 9.8; 5.1 (4.7–17)[d]	I: 12.2; 2.0 II: 18.8; 14.5 III: 32.5; 19.9	375 mg/m^2	q1w, 4 doses in total (infusion)	n.r.	[109]
34	Steroid-dependent nephrotic syndrome	PKs only from subgroup ($n = 5$)	NCA	12	12.7; 3.9 (5–19)[d]	n.r.	375 mg/m^2 (max. 500 mg)	Single dose (infusion)	n.r.	[110]
Tocilizumab										
35a	Polyarticular juvenile idiopathic arthritis	Comparison of 8 and 10 mg/kg regimen for patients <30 kg with 8 mg/kg for >30 kg	EDCA	32	6.9; 3.1	20.6; 5.8	<30 kg: 10 mg/kg	q4w (IV infusion)	n.r.	[28, 111]
35b				30	7.7; 2.6	22.4; 5.3	<30 kg: 8 mg/kg	q4w (IV infusion)		
35c				115	13.1; 2.8	49.3; 12.1	≥30 kg: 8 mg/kg	q4w (IV infusion)		
36[p]	Systemic juvenile idiopathic arthritis		EDCA	6	5.0 (2–7)	19.6; 4.29 (14.6–23.6)[d]	8 mg/kg	Single dose (IV infusion)	n.r.	[112, 113]

Table 3 continued

Study no.	Indication	Study information for PK evaluation	PK analysis	No. of individuals	Age (years)[a]	BW (kg)[b]	Dose	Dosing regimen (administration route[c])	ADA$^+$ (%)	Refs.
37[p]	Systemic juvenile idiopathic arthritis	Different number of patients for PK parameters (C_{max}: $n = 50$, $t_{½}$: $n = 23$)	NCA	56	8.3; 4.4	n.r.	8 mg/kg	q2w (IV infusion)	n.r.	[113, 114]
38a[p]	Systemic juvenile idiopathic arthritis	2 dose levels based on BW	EDCA	37	13.5; 2.9	49.2; 18.5	≥30 kg: 8 mg/kg	q2w (IV infusion)	2.8	[13, 113, 115]
38b[p]				38	6.6; 3.3	18.9; 5.4	<30 kg: 12 mg/kg	q2w (IV infusion)		

The reported parameters for studies described in this table are given in Table 4, using the 'Study no.' column for cross-reference. Information centered over multiple row applies to all the respective rows

ADA$^+$ anti-drug antibody positive, *AUC* area under the plasma concentration–time curve, *BW* body weight, *BSA* body surface area, C_{max} maximum concentration, C_{min} minimum concentration, *CL* clearance, *EDCA* exploratory drug concentration analysis, *gest.* gestational, *IM* intramuscular, *Ind. CMT* individual compartmental analysis, *IV* intravenous, *max.* maximum, *MMF* mycophenolate mofetil, n_{adult} number of adults, n_{paed} number of paediatric patients, *NCA* non-compartmental analysis, *n.r.* not reported, *od* once daily, *Pop. CMT* population compartmental analysis, *PK* pharmacokinetic, *qxw* every *x* weeks, *Refs.* references, *RSV* respiratory syncytial virus, *SC* subcutaneous, $t_{½}$ half-life, t_{max} time to C_{max}, V_d volume of distribution

[a] Presented in years as mean; standard deviation, or median (range) if not stated otherwise

[b] Presented in kg as mean; standard deviation, or median (range) if not stated otherwise

[c] As specified in study; some report more information

[d] Mean; standard deviation (range)

[e] For total population included in study (PK analysis only on subpopulation)

[f] Range of means

[g] With methotrexate

[h] Without methotrexate

[i] Range

[j] Median

[k] Mean

[m] Median (interquartile range)

[n] Parameters from model not reported, therefore summarised in Tables 3 and 4

[p] Data/parameters (partly) extracted from a review [113]

Table 4 Pharmacokinetic results from studies in Table 3 (performing exploratory drug concentration analysis or non-compartmental analysis)

Study no.	*AUC* (day·µg/mL)	C_{max} (µg/mL)	t_{max} (days after last dose[p,q])	C_{min} (µg/mL)	t_{min} (weeks after last dose[p,q])	$t_{½}$ (days)	CL or CL/*F*	V_d or V_d/*F*	*F* (%)
Adalimumab									
1a				Week 26: 10.4; 4.26	Week 26: 2				
				Week 52: 9.48; 5.61	Week 52: 2				
				Dose escalation to q1w, week 52: 15.3; 11.4	Dose escalation, week 52: 1				
1b				Week 26: 3.63, 2.5	Week 26: 2				
				Week 52: 3.51, 2.21	Week 52: 2				
				Dose escalation to q1w, week 52: 6.7; 3.5	Dose escalation, week 52: 1				
2	Single dose: 68.7, 50.1[a]	Single dose: 9.2; 4.1[a]	Single dose: 2.29; 2.58			Single dose: 6.63; 6.49	Single dose: 480; 200 mL/day[b]	Single dose: 3,500; 1,300 mL	
	Steady state: 84.1; 70.5[a]	Steady state: 12.8; 8.3[a]	Steady state: 1.43; 0.408			Steady state: 11.4; 16.8	Steady state: 1,280; 1,040 mL/day[b]	Steady state: 6,600; 5,400 mL	
3				With methotrexate:					
				Week 12 and/or 24: 7.9; 5.6 (71.2)[c] ($n = 11$)	2				
				Without methotrexate:					
				Week 12 and/or 24: 6.0; 6.1 (101)[c] ($n = 4$)	2				
4a				Without methotrexate: Steady state: 6.8[d]					
				With methotrexate: Steady state: 10.9[d]					
4b				Without methotrexate:					
				Steady state: 6.6[d]					
				With methotrexate:					
				Steady state: 8.1[d]					
5a				With methotrexate:					
				Week 16: 6.73 (0–13.2)[e]	Week 16: 2				
				Week 60: 14.3 (0–24.6)[e]	Week 60: 2				
				Without methotrexate:					
				Week 16: 2.77[k]					
				Week 60: 3.09[k]					
5b				With methotrexate:					
				Week 16: 10.4 (0–19.4)[e]	Week 16: 2				
				Week 60: 14.4 (0–21.6)[e]	Week 60: 2				
				Without methotrexate:					
				Week 16: 12.6[k]					
				Week 60: 8.55; 15.9					
Alemtuzumab									
6		6.5 (1.3–23.5)							n.a.

Table 4 continued

Study no.	*AUC* (day·μg/mL)	C_{max} (μg/mL)	t_{max} (days after last dose[p,q])	C_{min} (μg/mL)	t_{min} (weeks after last dose[p,q])	$t_{½}$ (days)	CL or CL/*F*	V_d or V_d/F	*F* (%)
Basiliximab									
7	157 (101–211) day·mg/mL[$]	First dose: 11.1 (7.48–19.8) Second dose: 14.8 (8.49–19.8)				7.24 (3.94–9.29)	127 (94–192) mL/day	1,070 (625–2,020) mL	n.a.
8a	101; 68	First dose: 6.7; 2.5, Second dose: 9.7; 3.9				10.1; 7.6	With MMF: 624; 288 mL/day[f] Without MMF: 1,010; 480 mL/day[f]		n.a.
8b	102; 42	First dose: 9.3; 8.3, Second dose: 8.7; 2.3				12.1; 5.0	With MMF: 528; 192 mL/day[f] Without MMF: 1,010; 624 mL/day[f]		n.a.
Bevacizumab									
9a	1,140 (839–1,370)	109 (90.8–117)		27.1 (35.4–18.9)	2	12.8 (9.9–12.9)	4.4 (3.7–6.0) mL/day/kg	75.1 (64.8–81.3) mL/kg	n.a.
9b	3,970 (966–4,770)	299 (230–425)		80.1 (44.7–117)	2	11.7 (4.4–14.6)	3.8 (3.1–15.5) mL/day/kg	63.4 (49.5–89.6) mL/kg	n.a.
Canakinumab									
10	580 (543–647)	12.4 (7.67–16.3)	2.16 (2–7.05)			23.7 (22.9–25.7)	131 (62.1–232) mL/day 3.7 (3.4–4.8) mL/day/kg	4,480 (2,300–7,670) mL 127 (127–158) mL/kg[g]	
11		0.174 (0.131–0.206) μg/mL/mg administered dose	1.82 (1.63–6.86)			15.7 (8.55–29.2)	233 (152–490) mL/day	4,950 (3,230–12,400) mL	
Cetuximab									
12a	66.6 (48)[h]			1.02	1		1,370; 984 mL/day/m^2	2,080; 666 mL/m^2	n.a.
12b	370 (21)[h]			16.8	1		408; 96 mL/day/m^2	1,860; 564 mL/m^2	n.a.
12c	738 (24)[h]			35.6	1		360; 120 mL/day/m^2	2,160; 362 mL/m^2	n.a.
12d	80.2 (23)[h]						960; 240 mL/day/m^2	2,140; 453 mL/m^2	n.a.
12e	293 (3)[h]			11.7	1		504; 24 mL/day/m^2	1,890; 262 mL/m^2	n.a.
12f	558 (38)[h]			27.2	1		480; 126 mL/day/m^2	2,180; 250 mL/m^2	n.a.
Cixutumumab									
13a	1,360; 882			59; 31	7 days		6; 2.88 mL/day/kg		n.a.
13b	1,930; 870			106; 57	7 days		5.28; 1.92 mL/day/kg		n.a.
Eculizumab									
14a	Induction: 871 Maintenance: 3,970	Induction: 147 Maintenance: 392		Induction: 104 Maintenance: 196	Induction: 24 h Maintenance: before dose				n.a.
14b	Induction: 920; 60.5[d] Maintenance: 4,160; 470[d]	Induction: 157; 9.8[d] Maintenance: 414; 36.7[d]		Induction: 109; 8.1[d] Maintenance: 205; 29.9[d]	Induction: day 1 Maintenance: before dose				n.a.

Table 4 continued

Study no.	*AUC* (day·μg/mL)	C_{max} (μg/mL)	t_{max} (days after last dose[p,q])	C_{min} (μg/mL)	t_{min} (weeks after last dose[p,q])	$t_{½}$ (days)	CL or CL/*F*	V_d or V_d/*F*	*F* (%)
Gemtuzumab ozogamicin									
15a[†]	1.93; 2.27	1.58; 1.16				1.28; 0.37	3,800; 3,800 mL/day	2,300; 1,200 mL	n.a.
							7,000; 7,200 mL/day/m^2	190; 100 mL/kg	
15b[†]	1.71; 2.0	2.14; 1.66				1.37; 0.76	6,500; 5,300 mL/day	11,200; 11,800 mL	n.a.
							7,000; 4,300 mL/day/m^2	480; 510 mL/kg	
15c[†]	2.26; 2.14	1.49; 0.80				2.19; 1.04	24,000; 45,000 mL/day	20,100; 15,500 mL	n.a.
							16,000; 33,000 mL/day/m^2	360; 280 mL/kg	
15d[†]	4.63; 1.57	3.11; 0.55				1.67; 0.31	2,900; 1,400 mL/day	6,300; 2,500 mL	n.a.
							1,700; 480 mL/day/m^2	110; 40 mL/kg	
15e[†]	5.58; 1.53	3.54; 0.83				4.71; 4.5	720; 480 mL/day	2,900; 2,700 mL	n.a.
							1,200; 480 mL/day/m^2	240; 220 mL/kg	
15f[†]	7.67; 6.79	3.76; 1.00				1.90; 1.28	1,400; 720 mL/day	3,900; 1,600 mL	n.a.
							1,900; 1,200 mL/day/m^2	170; 70 mL/kg	
15g[†]	4.25; 2.48	3.24; 1.19				2.58; 0.69	6,200; 7,200 mL/day	9,400; 6,600 mL	n.a.
							4,100; 5,000 mL/day/m^2	170; 120 mL/kg	
Infliximab									
16				Week 2: 16.7; 7.3	Week 2: 2				n.a.
				Week 6: 8.8; 7.1	Week 6: 4				
17		Steady state: 108.7 (94.4–133.8)[i]		Week 30: 1.8 (1.3–2.8)[i]	Week 30: 8	10.7 (7.4–15.2)[i]			n.a.
18a				2.7[j]	8				n.a.
18b				6.29[j]	8				n.a.
19a	133; 74.6	22.5		0.102	4	4.8[d]			n.a.
19b	993; 408	122		0.103	8	9.3[d]			n.a.
19c	2,430; 880	223		0.101	12	9.5[d]			n.a.
20a		Week 44: 54.9		Week 52: 0.051	8	6.9[j]			n.a.
20b		Week 44: 125		Week 52: 2.40	8	9.5[j]			n.a.
21a	746 (276–1,520)	81 (35–100)	2 h			5.1 (2.4–13)	2.64 (1.20–7.20) mL/day/kg	53 (22–88) mL/kg	n.a.
21b	547 (251–1,810)	75 (36–147)	2 h			7.3 (2.8–27.9)	3.6 (1.20–7.92) mL/day/kg	81 (30–202) mL/kg	n.a.
22		Week 2: 115.1 (86.6–129.3)[i]	1 h	Week 30:		10.8 (8.6–15.4)[i]			n.a.
		q8w, steady state: 89.4[j]	1 h	q8w: 1.9 (0.2–3.9)[i]	q8w: 8				
		q12w, steady state: 90.6[j]	1 h	q12w: 0.8[j]	q12w: 12				

Table 4 continued

Study no.	*AUC* (day·μg/mL)	C_{max} (μg/mL)	t_{max} (days after last dose[p,q])	C_{min} (μg/mL)	t_{min} (weeks after last dose[p,q])	$t_{½}$ (days)	CL or CL/*F*	V_d or V_d/F	*F* (%)
Motavizumab									
23a[‡]				First dose: 7.9[k]	30 days				
23b[‡]				First dose: 50.2 (2.76–106)[e]	30 days	24.4; 5.7			
				Fourth dose: 86.2 (0–194)[e]	30 days				
				Fifth dose: 95.9[k]	30 days				
				ADA$^-$:					
				89.0 (0–194)[e]	30 days				
				17.4 (0–45.2)[e]	90 days				
				4.1 (0–13.9)[e]	150 days				
				ADA$^+$:					
				9.5 (0–32.7)[e]	30 days				
				0 (0–0)[e]	90 days				
23c[‡]				First dose: 54.6 (16.5–87.2)[e]	30 days				
				Fourth dose: 86.2 (37.5–148)[e]	30 days				
24				Day 60: 8.02[k]	Day 60: 30 days				
				Day 150: 105.8[k]	Day 150: 30 days				
Natalizumab									
25	First dose: 346 (179–777)	First dose: 57.4 (40.5–114)	"Immediately after infusion"	First dose: 0 (0–3.3)	First dose: 4	First dose: 3.85 (2.03–7.11)	First dose: 418 (135–818) mL/day	First dose: 2,160 (668–4,460) mL	n.a.
	Third dose: 439 (109–759)	Third dose: 66.7 (42.0–164)		Third dose: 0 (0.0–6.1)	Third dose: 4	Third dose: 4.01 (1.98–10.9)	Third dose: 409 (179–1,270) mL/day	Third dose: 2,370 (771–4,850) mL	
Pagibaximab									
26		First dose:		First dose:	First dose: 2	20.5; 6.8 (19–25[m])	7.68–10.3 mL/day[m]	182–285 mL[m]	n.a.
		10 mg: 99.5		10 mg: 19.4					
		30 mg: 330		30 mg: 49.7					
		60 mg: 632		60 mg: 99.8					
		90 mg: 892		90 mg: 174					
		Second dose:		Second dose:	Second dose: 6				
		10 mg: 99.8		10 mg: 11.3					
		30 mg: 377		30 mg: 25.6					
		60 mg: 628		60 mg: 59.7					
		90 mg: 1,080		90 mg: 123					
27a		First dose: 939		First dose: 225	First dose: 7	17.6[k]	7.74 mL/day[k]	191 mL[k]	n.a.
		Second dose: 1,020		Second dose: 397	Second dose: 7				
		Third dose: 1,340		Third dose: 237	Third dose: 4				
27b		First dose: 1,140		First dose: 279	First dose: 7	14.5[k]	9.47 mL/day[k]	193 mL[k]	n.a.
		Second dose: 1,400		Second dose: 520	Second dose: 7				
		Third dose: 1,880		Third dose: 291	Third dose: 4				

Table 4 continued

Study no.	*AUC* (day·μg/mL)	C_{max} (μg/mL)	t_{max} (days after last dose[p,q])	C_{min} (μg/mL)	t_{min} (weeks after last dose[p,q])	$t_{½}$ (days)	CL or CL/*F*	V_d or V_d/F	*F* (%)
Palivizumab									
28	4,190 (2,370–6,240)[e]	374 (238–581)[e]	0.028 (0.021–0.042)[e]	41.9 (22.4–58.6)[e]	30 days	22.4 (9.9–56.7)[e]	4.1 (2.5–6.3) mL/day/kg[e]	110 (50.8–205) mL/kg[e]	n.a.
29a	487 μg/mL[k,$]	61.2[k]	1 h	11.2 [k]	30 days	22.6[k]			n.a.
29b	2,386 μg/mL[k,$]	303[k]	1 h	38.4 [k]	30 days	16.8[k]			n.a.
30a				12.5 (4.2–26.2)[e]	30 days	24[k]			
30b									
30c		First dose: 91.1; 3.8	2	First dose: 49.2 (13.5–132)[e]	30 days (for all doses)				
		Second dose: 150; 8.6	2	Second dose: 69.4; 4.3					
				Third dose: 69.5; 4.7					
				Fourth dose: 70.3; 5.3					
				Fifth dose: 73.4; 6.2					
31a	593 (unit n.r.)	28.6 (4.7–50.8)[e]	1 h	First dose: 6.8 (2.7–16.4)[e]	30 days	19.3–26.8[m]			n.a.
				Second dose: 11.9 (2.3–25.2)[e]	30 days				
31b	3,508 (unit n.r.)	154 (106–274)[e]	1 h	First dose: 36.1 (18.6–101.6)[e]	30 days				n.a.
				Second dose: 45.2 (21.4–99.5)[e]	30 days				
31c	5,295 (unit n.r.)	313 (5.8–618)[e]	1 h	First dose: 60.6 (21.4–149.8)[e]	30 days				n.a.
				Second dose: 70.7 (20.2–112.6)[e]	30 days				
Rituximab									
32a		First cycle: 299; 19		107; 32	3 weeks	29; 7			n.a.
		Second cycle: 384; 25							
32b		First cycle: 245; 31		55; 8	3 weeks	26; 3			n.a.
		Second cycle: 321; 32							
33		Fourth dose: 447; 29 (all groups)		63; 7	1 month				n.a.
34	3,470; 2,210	220; 78.9	"Just after infusion"	27.4; 18.4	30 days	14.6; 5.2	140; 71.3 mL/day/mm$^{2,\$}$	2,220; 370 mL/m^2	n.a.
				3.0; 4.4	90 days				
Tocilizumab									
35a	Week 12: 968; 254	Week 12: 175; 32		Week 12: 2.35; 3.59	4				n.a.
35b	Week 12: 702; 218	Week 12: 140; 25		Week 12: 0.95; 2.07	4				n.a.
35c	Week 12: 1,230; 361	Week 12: 182; 37		Week 12: 7.49; 8.20	4				n.a.
36	All: 433; 137	96; 21.2							n.a.
	2–5 years: 278; 108 day·mg/mL[$]						2–5 years: 0.78[$]; 0.34 mL/kg		
	6–18 years: 221; 40.8 day·mg/mL[$]						6–18 years: 0.89[$]; 0.18 mL/kg		

Table 4 continued

Study no.	*AUC* (day·µg/mL)	C_{max} (µg/mL)	t_{max} (days after last dose[p,q])	C_{min} (µg/mL)	t_{min} (weeks after last dose[p,q])	$t_{½}$ (days)	CL or CL/*F*	V_d or V_d/*F*	*F* (%)
37	Week 6: 1,270; 496	Week 6: 209; 68.3		Week 2: 20.2; 12.4	Week 2: 2	5.1; 1.3			n.a.
				Week 4: 34.3; 17.2	Week 4: 2				
				Week 6: 43.0; 20.5	Week 6: 2				
				Week 18: 56.7; 18.8	Week 18: 2				
38a	1,340; 409	226; 54.5		Week 12: 69; 25	Week 12: 2	18.4–22.7[n]			n.a.
				Week 52: 65; 31	Week 52: 2				
38b	1,350; 426	263; 54.1		Week 12: 71; 31	Week 12: 2	19.2–23[n]			n.a.
				Week 54: 77; 28	Week 52: 2				

The 'Study no.' column refers to the study number attributed in Table 3 for cross-referencing to studied dosing regimens and populations

Empty cells indicate that values were not reported. All parameter values are presented as mean; SD, or median (range) if not else stated (SD and ranges correspond to between subject variability in this table)

%CV percentage coefficient of variation, ADA^+ anti-drug antibody positive, ADA^- anti-drug antibody negative, *AUC* area under the plasma concentration–time curve, *CL* clearance, C_{max} maximum concentration, C_{min} minimum concentration, *F* bioavailability, $t_{½}$ half-life, t_{max} time to C_{max}, t_{min} time to C_{min}, *MMF* mycophenolate mofetil, *n.a.* not applicable (intravenous administration), *n.r.* not reported, *qxw* every *x* weeks, *SD* standard deviation, V_d volume of distribution

[a] Dose-normalised to 40 mg

[b] Allometrically scaled to 70 kg

[c] Mean; SD (%CV)

[d] Used central/distribution measure not reported

[e] Mean (range)

[f] Normalised to 1.73 m^2

[g] Transformed using individual body weight

[h] Mean (%CV)

[i] Median (interquartile range)

[j] Median

[k] Mean

[m] Range of means

[n] Range

[p] If not else stated

[q] As specified in study

[$] Reported unit likely wrong

[†] Only first dose reported here because the second was merged over all age groups

[‡] Compartmental analysis but parameters not reported

study characteristics and parameter estimates have been systematically collated for the Ind. CMT and Pop. CMT in Tables 5 and 6, respectively. To all these four tables, a 'Study no.' column has been added to enable cross-referencing of studies and groups in Tables 3 and 5 to the corresponding parameters in Tables 4 and 6 (these 'study numbers' are also used in Figs. 1, 2 and 3).

The number of studies per mAb was found to vary highly; ten studies were found for infliximab whereas for many mAbs only one study was published. Similarly, the number of individuals per pharmacokinetic analysis showed a large range from three to 4,316. As is evident from Tables 4 and 6, only a small fraction of the reviewed studies provided a complete summary of the pharmacokinetic characteristics; this is not only due to the analysis complexity but parameters also seem to have been omitted. As a result of the varying analysis complexity, and many studies being more clinically orientated, the parameters have been described in a rather heterogeneous fashion, e.g. as an estimate for the studied population, or scaled to a BW of 70 kg. This heterogeneity was handled differently depending on the pharmacokinetic parameter and is, thus, explained in each of the following subsections.

4.1 Absorption

4.1.1 General Principles and Mechanisms

Oral administration of mAbs is generally limited by low permeability and degradation throughout the gastrointestinal tract [9]. mAbs are, thus, administered intravenously, subcutaneously or intramuscularly. The mechanisms of absorption after subcutaneous and intramuscular administration are not yet fully understood [38]. Based on the molecular properties of mAbs and animal studies of subcutaneously administered biotherapeutics (excluding mAbs), convective transport via the lymphatic system is considered to be the primary pathway for subcutaneous absorption, meaning that they move together with fluids [38]. No information was found regarding intramuscular administration specifically. For small molecules, however, intramuscular administration has been described as risky, especially for small children since the blood flow to muscle and muscle mass may vary considerably [10].

Factors identified to influence absorption and bioavailability (F) of biotherapeutics (not including mAbs) include (i) site of administration; (ii) physiological factors (e.g. blood and lymph flow, catabolism at the site of injection and physical activity); and (iii) formulation-related factors (e.g. pH and injection volume) [38]. The impact of these factors on absorption of mAbs still needs to be elucidated considering also their inherent Fc structure and the potential influence of FcRs on absorption. Studies in rats suggest that the neonatal FcR (FcRn; see Sect. 4.3.1 for further details) plays an important role in the absorption of mAbs [39, 40]. It is also unclear whether physiological changes during growth (e.g. differences in blood and/or lymph flow) will affect the extent and/or rate of absorption in children.

4.1.2 Summary of Absorption-Related Parameters

Few of the retrieved studies characterised mAb absorption. One reason for the limited information is, naturally, that many mAbs were not extravascularly administered. Another reason may be a sparse data situation, commonly seen in late-stage clinical trials and data from daily practice, potentially preventing adequate estimation of absorption-associated parameters. Indeed, for omalizumab the absorption rate constant (k_a) after subcutaneous administration was obtained from adult healthy volunteers and fixed to that value during further pharmacokinetic model development [41].

After intramuscular administration, the estimate of k_a was 1.0 day^{-1} (palivizumab); this is a higher value, thus indicating quicker absorption than in adults (0.37 day^{-1}) [42]. The population in this study was very young (preterm to <2 years). Whether the differences in k_a depended on, for example, differences in blood flow to muscle or other physiological differences, remains to be elucidated. The median/mean time to C_{max} (t_{max}) after subcutaneous administration (by NCA) was rather similar across studies, ranging from 1.43 to 2.29 days ($n_{groups} = 4$). However, the within-mAb variability was large, e.g. ranging from 1.63 to 6.86 days for canakinumab [80, 81]. One study reports a t_{max} after intramuscular administration, which was in agreement with the report after subcutaneous administration (2 days) [106].

Regarding F, two studies reported F after subcutaneous (23.4 and 53–71 %) [116, 121] and one after intramuscular (69 %) administration [42]. These values seem consistent with results for adults after subcutaneous administration (49.1–74.7 % [3]), although it is difficult to draw clinical conclusions based on this small number of studies. Overall, to date, evidence is too limited to infer whether absorption characteristics are similar in children and adults; more studies as well as more sophisticated data analysis methods are required (see below).

4.2 Distribution

4.2.1 General Principles and Mechanisms

The transfer of mAbs across cell membranes is limited due to their large molecular mass and hydrophilic character. Hence, the volume of distribution (V_d) values in adults are in general reported to be small and mAbs are presumed to

Table 5 Key features of pharmacokinetic studies (individual or population compartmental analysis) of monoclonal antibodies in children, regardless of its legal status (i.e. approved, in development, off-label use or withdrawn; hence, Table 5 includes monoclonal antibodies additional to those in Tables 1 and 2)

Study no.	Indication	Study information for PK evaluation	PK analysis	No. of individuals	Age (years)[a]	BW (kg)[b]	Dose	Dosing regimen (administration route[c])	ADA$^+$ (%)	Refs.
AMG 317										
39	Asthma and healthy volunteers	Pooled analysis of 4 studies including mostly adults but also adolescents. CL and V_1 allometrically scaled to 80 kg. k_a normalised to 40 years	Pop. CMT	270	36.3; 12.8 (12–64)[d]	86.1; 22.1 (44–169)[d]	10, 30, 75, 100, 150, 300, 600 or 1,000 mg	Single dose (IV or SC), or q1w for 4 weeks (SC), or q1w for 12 weeks (SC)	Included in model but proportion n.r.	[116]
Basiliximab										
40a	Prevention of acute renal transplant rejection	2 parts in study with 2 dose strategies. The parts were pooled for analysis of CL, V_{ss} and $t_{½}$. Parameters reported for 2 age groups	Ind. CMT	18 (part 1)	1–11[e,f] ($n = 25$)	9–37[f]	Part 1: 12 mg/m^2	Days 0 and 4 (IV bolus)	5.5	[13, 60]
							Part 2: 10 mg			
40b				19 (part 2)	12–16[e,f] ($n = 14$)	<52	Part 1: 12 mg/m^2	Days 0 and 4 (IV bolus)		
							Part 2: 20 mg			
Bevacizumab										
41	Osteosarcoma		Pop. CMT	26	12.2 (6.8–18.1)	54.9; 23.4 (22.1–110)[d]	15 mg/kg	Days relative to transplantation: −3, 22 and 36 (IV)	n.r.	[117]
Daclizumab										
42a				18	3 (0.9–5)[g]	12 (8–17)[g]	1 mg/kg	Day before transplantation, thereafter q2w. 5 doses in total (15–60 min IV infusion)		
42b	Prevention of acute renal transplant rejection	Parameters reported for 3 age groups	Pop. CMT	18	9 (6–12)[g]	29 (16–48)[g]	1 mg/kg	Day before transplantation, thereafter q2w. 5 doses in total (15–60 min IV infusion)	34	[118]
42c				25	15 (13–17)[g]	52 (29–90)[g]	1 mg/kg	Day before transplantation, thereafter q2w. 5 doses in total (15–60 min IV infusion)		
Infliximab										
43	Crohn's disease		Pop. CMT	5	16 (15–18)	50 (43–61)	4.5–5.3 mg/kg[f]	Multiple doses, time since last dose varying (2 h IV infusion)	n.r.	[46]
44	Crohn's disease	Same data as in Hyams et al. [99]. Combined model for adults and children available; here only estimates from child data reported. The effect of ADAs on PKs was not evaluated in study due to too few ADA$^+$	Pop. CMT	112	13 (6–17)	43.8; 14.6 (20.4–97.7)[d]	5 mg/kg	Weeks 0, 2 and 6, thereafter q8w or q12w (IV infusion)	2.7	[50]

Table 5 continued

Study no.	Indication	Study information for PK evaluation	PK analysis	No. of individuals	Age (years)[a]	BW (kg)[b]	Dose	Dosing regimen (administration route[c])	ADA$^+$ (%)	Refs.
45	Polyarticular juvenile rheumatoid arthritis	Same data as in Ruperto et al. [101]	Pop. CMT[h]	117	4–17[f]	n.r.	3 or 6 mg/kg	Weeks 0, 2 and 6, thereafter q8w (IV infusion)	Included in model but proportion n.r.	[59]
46	Ulcerative colitis, Crohn's disease, polyarticular juvenile rheumatoid arthritis and Kawasaki disease	Pooled analysis of previously reported paediatric trials [13, 23, 98, 99, 101] and 1 trial of adults with ulcerative colitis	Pop. CMT	$n_{paed} = 305$ $n_{adult} = 483$	0.167–17[f] (paediatric patients)	n.r.	5 mg/kg	q8w (IV infusion)	Included in model but proportion n.r.	[119]
Motavizumab										
47	Prophylaxis of RSV infection	Pooled analysis of 6 paediatric studies and 1 study of adults	Pop. CMT	$n_{paed} = 4{,}316$ $n_{adult} = 30$	<24 months[f] (paediatric subgroup)	n.r.	3 or 15 mg/kg	Every 30 days, 1–5 doses in total (IM)	n.r.	[120]
Omalizumab										
48	Allergic asthma	Pooled analysis of adults and paediatrics	Ind. CMT	1,950	n.r.	n.r.	n.r.	n. r. (SC)	n.r.	[121]
49	Allergic asthma	Pooled analysis on 5 clinical studies of adolescents and adults	Pop. CMT	1,928	12–79[f] (not separate for paed.)	40–150[f]	150–375[f] mg	Single dose, q2w or q4w. Dose selection based on BW and baseline IgE (SC)	n.r.	[58]
50	Allergic asthma	Same studies as in Lowe et al. [58] + 4 additional studies (e.g. paediatric studies >5 years). Number of subjects also includes patients on placebo used for IgE part of model	Pop. CMT	3,095	5–79[f] (not separate for paed.)	19–150[f]	150–375[f] mg	Single dose, q2w or q4w. Dose selection based on BW and baseline IgE (SC)	n.r.	[41]
Pagibaximab										
51	Prevention of *Staphylococcus aureus*-caused sepsis		Ind. CMT	100	"Infants"	n.r.	10–90 mg/kg	1–3 doses in total (IV infusion)	n.r.	[64]
Palivizumab										
52	Chronic lung disease or RSV infection	Adult PK model used as prior knowledge in model development	Pop. CMT	1,684	Pre-term to <24 months[f]	5.64 (0.92–16.3)	3, 5,10, 15 or 30 mg/kg	q4w, up to 5 doses (IV or IM)	Considered for model, but proportion n.r.	[42]
Rituximab										
53	Immune thrombocytopenic purpura or Evans syndrome	Evaluated at week 1 ($n = 14$) and/or week 4 ($n = 11$) ($n = 10$ in both)	Ind. CMT	15	11.2 (2.6–18.3)	n.r.	375 mg/m^2	q1w, 4 doses in total (IV infusion)	n.r.	[122]

Table 5 continued

Study no.	Indication	Study information for PK evaluation	PK analysis	No. of individuals	Age (years)[a]	BW (kg)[b]	Dose	Dosing regimen (administration route[c])	ADA$^+$ (%)	Refs.
Teplizumab										
54	Type 1 diabetes mellitus	3 dose levels evaluated	Ind. CMT	417[b]	8–35[f]	n.r.	cumulative dose: 9,034 μg/m^2 2,985 μg/m^2 2,985 μg/m^2	Single or 14-day course of escalating doses (IV infusion)	Treated: 77 Placebo: 13	[123, 124]

The reported parameters for studies described in this table are given in Table 6, using the 'Study no.' column for cross-reference. Information centered over multiple row applies to all the respective rows

ADA anti-drug antibody, *ADA*$^+$ ADA positive, *BW* body weight, *CL* clearance, *IgE* immunoglobulin E, *Ind.* individual, *CMT* compartmental analysis, *IM* intramuscular, *IV* intravenous, k_a absorption rate constant, n_{adult} number of adults, n_{paed} number of paediatric patients, *n.r.* not reported, *Paed.* paediatric population, *Pop. CMT* population compartmental analysis, *PK* pharmacokinetics, *qXw* every *x* weeks, *Refs.* references, *RSV* respiratory syncytial virus, *SC* subcutaneous, *SD* standard deviation, $t_{½}$ half-life, V_1 central volume of distribution, V_{ss} volume of distribution at steady state

[a] Presented in years as mean; SD, or median (range) if not stated otherwise

[b] Presented in kg as mean; SD, or median (range) if not stated otherwise

[c] As specified in study; some report more information

[d] Mean; SD (range)

[e] For total population included in study

[f] Range

[g] Mean (range)

[h] PK model or model development not fully reported

be restricted to vascular and extracellular fluid (ECF) [3, 4, 6, 7]. mAbs may reach the intracellular space by pinocytosis or via receptor-mediated endocytosis (RME, i.e. internalisation of the mAb–target/mAb–FcR complex) [43]. Within the cell, it either undergoes degradation or is recycled to the ECF or blood by the FcRn (discussed further in Sect. 4.3.1). Distribution into the brain is constrained by low transport across the blood–brain barrier (BBB). IgG molecules in general are effluxed from the brain, a mechanism potentially mediated also by the FcRn [44]. To our knowledge, there is so far no information on the influence of the FcRn (expression/efficacy) on the overall mAb distribution but, considering the potential effects on absorption, one could hypothesise that it would also affect distribution.

mAb concentration–time profiles after intravenous administration commonly follow a bi-exponential decay, often described by a two-compartment disposition model [4]. After subcutaneous administration, however, the profiles typically display mono-exponential decline as a result of slow absorption, masking the first (relatively) rapid distribution phase [4]. As mentioned, convection is believed to be the primary mechanism of transport [3, 4, 6, 7, 9]. The rate of transport is hence determined by the rate of fluid movement and the sieving effect by paracellular pores [6], and mAbs show, in general, slow transfer between central and peripheral compartments [3]. In summary, the overall distribution of mAbs may be affected by the rate of extravasation/pore size, rate/flow/proportion of ECF, the degree of binding in tissue, RME [6, 9] and, potentially, expression/efficacy of FcRn.

4.2.2 *Developmental Aspects*

During growth and development, children undergo changes in, for example, body composition, membrane permeability and plasma protein concentrations [10]. The relative total body water decreases from 80–90 % to approximately 60 % over the first 5 months, and thereafter remains relatively constant [45]. The main contributing factor is a decrease in ECF, which is approximately 45 % at birth, 26 % at 1 year and 18 % when an adult [45]. It is reasonable to believe that these changes influence V_d, especially in children <1 year, since mAbs are considered to be distributed mainly in the vascular and ECF space, although further research is needed to explore to what extent.

Children <1 year have reduced concentrations of albumin, globulins and α_1-acid glycoprotein and, hence, a reduced total plasma protein concentration (neonates: 59 g/L vs. adults: 72 g/L) [10]. Even though a reduced plasma protein concentration and other known factors (e.g. higher BBB permeability) may play an important role in the distribution of small molecules [10], it will probably be of less

Table 6 Pharmacokinetic and pharmacokinetic–pharmacodynamic results from studies in Table 5 reporting individual and/or population compartmental analyses

Study no.	k_a (day^{-1}) *BSV/IOV* [Cov. effect]	*F* *BSV/IOV* [Cov. effect]	CL or CL/*F* *BSV/IOV* [Cov. effect]	Q or k_{12}/k_{21} *BSV/IOV* [Cov. effect]	V_1 or V_1/F *BSV/IOV* [Cov. effect]	V_2, V_2/F or V_{ss} *BSV/IOV* [Cov. effect]	TMDD/PD *BSV/IOV* [Cov. effect]
AMG 317							
39[†]	0.185 (0.168–0.187)[a,b] *BSV: 38 % (32–40 %)*[a] [↑ w. ↓ age]	0.234 (0.234–0.250)[a]	840 (830–886) mL/day[a,c] *BSV: 40 % (37–43 %)*[a] [Allometrically scaled, ↑ if ADA$^+$]	Q: 658 (626–689) mL/day[a] *BSV: 44 % (44–53 %)*[a]	1,780 (1,700–1,800) mL[a,c] *BSV: 28 % (25–29 %)* [a] [Allometrically scaled, ↑ if IV administration, ↑ w. ↓ formulation strength]	V_2: 5,030 (4,890–5,340) mL[a]	R_{max}: 304 (302–322) ng/mL[a] *BSV: 24 % (20–24 %)*[a] [↑ if ADA$^+$] K_{SS}: 51.7 (48.3–52.7) ng/mL[a] K_{int}: 0.167 (0.164–0.172) 1/h[a]
Basiliximab							
40a	n.a.	n.a.	408; 144 mL/day[d] [Independent of age and BW (within age group)]	n.r.	2,100; 900 mL[d] [↑ w. ↑ age, ↑ BW, and ↑ BSA]	V_{ss}: 4,800; 2,100 mL[d] [Independent of age and body size (within age group)]	
40b	n.a.	n.a.	744; 456 mL/day[d] [Independent of age and BW (within age group)]	n.r.	3,600; 1,600 mL[d]	V_{ss}: 7,800; 5,100 mL[d]	
Bevacizumab							
41	n.a.	n.a.	5.16 (4.36–5.74) mL/day/kg[e] *BSV:18.4 % (8.4–33.9 %)*[e], *IOV:18.2 % (13.3–22.6 %)*[e] [↑ w. ↑ BW, and ↑ w. ↓ BMI percentile]	k_{12}: 5.33 (4.49–6.43) 1/h[e] *BSV: 25 % (12.7–37.3 %)*[e] k_{21}: 8.04 (6.00–10.0) 1/h[e] *BSV: 49.8 % (15.1–87.7 %)*[e]	62.7 (57.5–69.0) mL/kg[e], *BSV: 13.2 % (9.0–17.6 %)*[e], *IOV: 4.7 % (1.6–7.4 %)*[e] [↑ w. ↑ BW, and ↑ w. ↓ BMI percentile]	n.r.	
Daclizumab							
42a	n.a.	n.a.	126 (57–194) mL/day[f,g] *BSV: 30 %* [↑ w. ↑ BW, and ↑ for Black ethnicity]	Q: 148 mL/day[h]	920 (430–1,330) mL[f,g] *BSV: 40 %* [↑ w. ↑ BW, and ↓ for Black ethnicity]	V_2: 1,360 mL[h]	
42b	n.a.	n.a.	259 (172–434) mL/day[f,g] *BSV: 30 %* [↑ w. ↑ BW, and ↑ for Black ethnicity]		1,680 (630–3,180) mL[f,g] *BSV: 40 %* [↑ w. ↑ BW, and ↓ for Black ethnicity]		
42c	n.a.	n.a.	348 (145–696) mL/day[f,g] *BSV: 30 %* [↑ w. ↑ BW, and ↑ for Black ethnicity]		2,490 (460–5,920) mL[f,g] *BSV: 40 %* [↑ w. ↑ BW, and ↓ for Black ethnicity]		
Infliximab							
43	n.a.	n.a.	199.2 (40) mL/day[g,i]		3,000 (13) mL[g,i]		

Table 6 continued

Study no.	k_a (day^{-1}) *BSV/IOV* [Cov. effect]	*F* *BSV/IOV* [Cov. effect]	CL or CL/*F* *BSV/IOV* [Cov. effect]	Q or k_{12}/k_{21} *BSV/IOV* [Cov. effect]	V_1 or V_1/F *BSV/IOV* [Cov. effect]	V_2, V_2/F or V_{ss} *BSV/IOV* [Cov. effect]	TMDD/PD *BSV/IOV* [Cov. effect]
44	n.a.	n.a.	5.43 (2.8) mL/day/kg *BSV: 25.2 % (25.4)* *IOV: 21.9 % (22.9)* [↑ w. ↓ BW, and ↑ w. ↓ serum albumin]	Q: 3.52 (20.1) [mL]/day/kg	54.2 (2.1) mL/kg *BSV: 16.3 % (30.6)* [↑ w. ↓ BW]	V_2: 29.2 (7.0) mL/kg *BSV: 34.9 % (44.0)* [↑ w. ↓ BW]	
45	n.a.	n.a.	6; 2 (2–16) mL/day/kg[g,j] [↑ w. ↓ age, ↑ w. ↑ resting energy expenditure/kg]	n.r.	n.r.	V_{ss}: 100; 40 (30–230) mL/kg[g,j] [↑ w. ↓age]	
46	n.a.	n.a.	294 (2.7) mL/day[k] [BW, ADA and serum albumin on PK, n.r. for which parameters or direction of impact. Independent of age and disease type]	Q: 72 (53) mL/day[k] [see CL]	3,330 (1.6) mL[k] [see CL]	V_2: 1,140 (25) mL[k] [see CL]	
Motavizumab							
47			n.r. *BSV: 25 %* [related to PMA (n.r. which direction), ↑ w. ↑ BW, ↑ if chronic lung disorder]	n.r.	n.r.	n.r. [related to PMA (n.r. which direction), ↑ w. ↑ BW]	
Omalizumab							
48		0.53–0.71	3.5; 1.7 mL/day/kg		95.6; 35 mL/kg		
49[†]	0.458; 0.0626[m] *BSV: 141 %*	n.r.	Free omalizumab: 208; 3.38 mL/day[k,m,n] *BSV: 40 %* [↑ w. ↑ BW] Complex: 832; 34.4 mL/day[k,m,n] *BSV: 26 %* [↑ w. ↑ BW] IgE: 3,850; 155 mL/day[k,m,n] *BSV: 23 %* [↑ w. ↑ BW, ↑ w. ↑ baseline IgE]		Free omalizumab & IgE: 9,330; 147 mL[k,m] *BSV: 22 %* [↑ w. ↑ BW] Complex: 6,310; 196 mL[k,m] *BSV: 26 %* [↑ w. ↑ BW]		IgE production rate: 1,220; 49.9 μg/day[m,n] *BSV: 30 %* [↑ w. ↑ BW, ↑ w. ↑ baseline IgE] K_d: 1.81; 0.0808 nmol/L[m,n] *BSV: 31 %* [↑ w. ↑ baseline IgE] Change in K_d: 0.0902; 0.0108 [m,n]

Table 6 continued

Study no.	k_a (day^{-1}) *BSV/IOV* [Cov. effect]	*F* *BSV/IOV* [Cov. effect]	CL or CL/*F* *BSV/IOV* [Cov. effect]	Q or k_{12}/k_{21} *BSV/IOV* [Cov. effect]	V_1 or V_1/F *BSV/IOV* [Cov. effect]	V_2, V_2/F or V_{ss} *BSV/IOV* [Cov. effect]	TMDD/PD *BSV/IOV* [Cov. effect]
50[†]	0.446 (3.2)[‡] *BSV: 57 % (7.9)*[‡]	n.r.	Free omalizumab: 206 (2.1) mL/day[k] *BSV: 37 % (11)* [↑ w. ↑ BW, ↑ w. ↑ BMI, ↑ ethnic group other than Caucasian] Complex: 535 (4.3) mL/day[k] *BSV: 36 % (38)* [↑ w. ↑ BW] IgE: 2,870 (4.3) mL/day[k] *BSV: 45 % (31)* [↑ w. ↑ BW, ↑ w. ↓ baseline IgE]		Free omalizumab and IgE: 8,620 (1.4) mL[k] *BSV: 26 % (23)* [↑ w. ↑ BW, ↓ if <12 years] Complex: 7,150 (1.8) mL[k,‡] *BSV: 21 % (13)*[‡] [↑ w. ↑ BW]		Prior IgE production rate: 967 (4.4) µg/day *BSV: 56 % (20)* [↑ w. ↑ baseline IgE, ↓ if <12 years, ↓ if female, ↑ if Black or Oriental, ↓ if other ethnic group] New IgE production rate: 253 (13) µg/day *BSV: 73 % (21)* [↑ w. ↑ BW, ↑ w. ↑ baseline IgE, ↓ if female, ↑ if <12 years, ↑ if Black, ↓ if other ethnic group] Change in IgE production rate: 53.8 (8.4) %/years [↑ w. ↑ BW, ↑ w. ↑ baseline IgE, ↓ if <12 years] K_d: 2.15 (4.7) nmol/L *BSV: 23 % (18)* [↑ w. ↑ baseline IgE, ↑ if < 12 years, ↓ if ethnic group other than Caucasian] Change in K_d: 0.0532 (24)
Pagibaximab							
51	n.a.	n.a.	10.7 mL/day[p]	n.r.	75 mL[p]	V_2: 138 mL[p]	
Palivizumab							
52	1.01 (13.10) (0.691–1.33)[q]	0.694 (3.13) (0.631–0.733)[q]	198 (3.96) (197–198) mL/day[k,q,r] *BSV: 49.8 %* [allometrically scaled, ↓ w. ↓ PMA, ↑ if chronic lung disease, ↑ if ADA[+], ↑ if ethnic group other than Caucasian]	Q: 879 (8.37) (856–967) mL/day[k,q] [allometrically scaled]	4,090 (3.2) (3,508–4,321) mL[k,q] *BSV: 61.6 %* [allometrically scaled, ↑ if Hispanic]	V_2: 2,230 (3.83) (1,694–2,842) mL[k,q] [allometrically scaled]	
Rituximab							
53	n.a.	n.a.		k_{12}[t]: week 1, 2–9 years: 0.36 (0.30–0.53) l/h week 1, 10–18 years: 0.29 (0.20–1.03) l/h week 4, 2–9 years: 0.17 (0.09–0.20) l/h week 4, 10–18 years: 0.29 (0.17–0.69) l/h	week 1, 2–9 years: 54 (43–76) mL/kg week 1, 10–18 years: 52 (35–73) mL/kg week 4, 2–9 years: 62 (54–74) mL/kg week4, 10–18 years: 49 (35–62) mL/kg		

Table 6 continued

Study no.	k_a (day^{-1}) *BSV/IOV* [Cov. effect]	*F* *BSV/IOV* [Cov. effect]	CL or CL/*F* *BSV/IOV* [Cov. effect]	Q or k_{12}/k_{21} *BSV/IOV* [Cov. effect]	V_1 or V_1/F *BSV/IOV* [Cov. effect]	V_2, V_2/F or V_{ss} *BSV/IOV* [Cov. effect]	TMDD/PD *BSV/IOV* [Cov. effect]
Teplizumab							
54	n.a.	n.a.	2,300 (33.1) mL/day[s] [↑ if ADA^+]		3,400 mL[h]	V_2: 6,900 mL[h] V_{ss}: 10,400 mL[h]	

The 'Study no.' column refers to the study number attributed in Table 5 for cross-referencing to the dosing regimens and populations of studies

All parameters are presented as estimate [RSE, % (precision)] if not stated otherwise. BSV and IOV are reported in italics and expressed as %CV. The covariate effects (if any) are presented within the brackets, with arrows indicating in which direction the parameter changes. If several fixed-effects parameters are reported in one cell the estimates relating to that parameter are indented below it

%CV percentage coefficient of variation, *ADA* anti-drug antibody, ADA^+ ADA positive, *BMI* body mass index, *BSA* body surface area, *BSV* between-subject variability, *BW* body weight, *CI* confidence interval, *CL* clearance, *Cov.* covariate, *F* bioavailability, *IgE* immunoglobulin E, *IOV* inter-occasion variability, *IV* intravenous, k_{12}/k_{21} intercompartmental rate constants, k_a absorption rate constant, K_d binding dissociation constant, K_{int} internalisation rate constant of drug-receptor complex, K_{ss} quasi-steady-state constant (see original publication for more details), *n.a.* not applicable (intravenous administration), *n.r.* not reported, *PMA* post-menstrual age, *PD* pharmacodynamic, *PK* pharmacokinetic, *Q* inter-compartmental clearance, R_{max} total receptor concentration, *RSE* relative standard error, *SD* standard deviation, $t_{½}$ half-life, *TMDD* target mediated drug disposition, V_1 central volume of distribution, V_2 peripheral volume of distribution, V_{ss} volume of distribution at steady state, *w.* with

[a] Estimate [90 % CI (precision)]

[b] Normalised to 40 years

[c] Normalised to 80 kg

[d] Mean; SD (variability)

[e] Median estimate [95 % CI (precision)] from bootstraps

[f] Median [range (variability)]

[g] Empirical Bayes estimates

[h] Estimate

[i] Median [%CV (variability)]

[j] Mean; SD (range) (variability)

[k] Normalised to 70 kg

[m] Estimate; standard error of the mean (precision)

[n] Normalised to IgE concentration of 365 ng/mL

[p] Mean

[q] Estimate (RSE, %) [95 % CI (precision)]

[r] Normalised to 40 weeks PMA

[s] Estimate (%CV, variability or precision, not stated)

[t] Calculated using reported $t_{½}$

[†] TMDD model

[‡] Fixed parameter

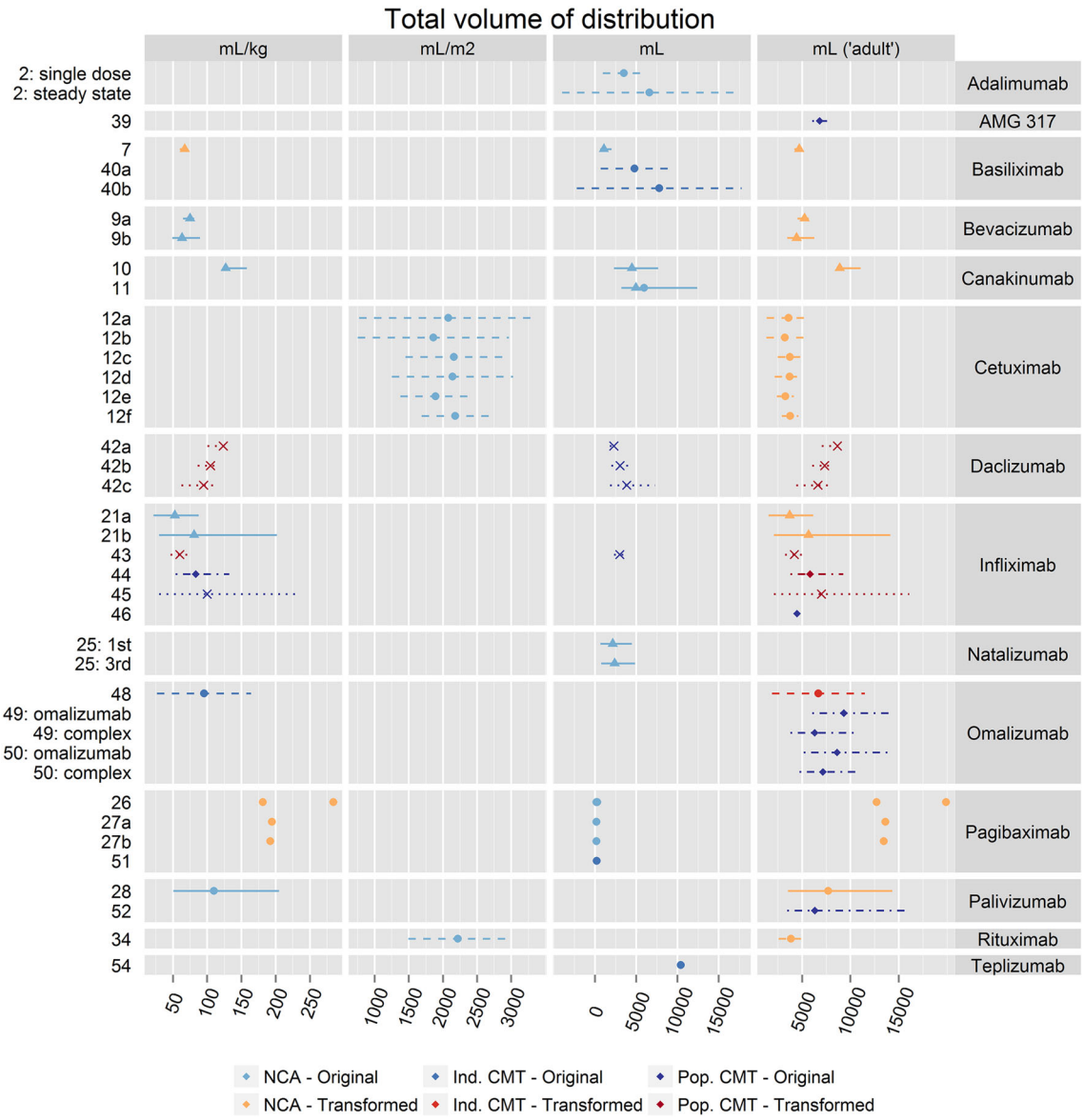

Fig. 2 Estimate and variability between individuals of V_d/V_{tot} values (*x*-axis) within and across monoclonal antibodies. The *numbers* on the *y*-axis refer to the number assigned in the 'Study no.' column of Tables 3 and 5. First panel: V_d/V_{tot} in mL/kg; second panel: V_d/V_{tot} in mL/m^2; third panel: V_d/V_{tot} in mL (non-scaled value); fourth panel: V_d/V_{tot} in mL (scaled to 'reference adult'). The *colours* show (i) the type of pharmacokinetic analysis; and (ii) *blue shades* represent the values/units reported in the original publications, whereas values with *red shades* have been transformed/normalised using the reported body weight or body surface area (see Sect. 4.2.3 for full explanation). *Points* indicate the mean, *dashed lines* indicate the 95 % CI calculated based on reported standard deviation and the mean, *triangles* indicate the median, *solid lines* indicate the range, *diamonds* indicate the estimate for typical individual (Pop. CMT), *dot-dashed lines* indicate the 95 % CI calculated based on reported between-subject variability, *crosses* indicate the mean or median EBEs (Pop. CMT), and *dotted lines* indicate the range of EBEs or 95 % CI calculated based on the coefficient of variation of EBEs. *CI* confidence interval, *EBEs* empirical Bayes estimates, *Ind. CMT* individual compartmental analysis, *NCA* non-compartmental analyses, *Pop. CMT* population compartmental analysis, V_d volume of distribution, V_{tot} total volume

clinical importance for mAbs due to their molecular properties, as previously discussed.

4.2.3 Summary of Distribution-Related Parameters

Consistent with observations in adults, the mAb concentration–time profiles in the paediatric population have predominantly been described using two-compartment disposition models, except for omalizumab which was modelled with a one-compartment model (subcutaneously administered; see also Sect. 4.2.1). A one-compartment model was also used in one out of four infliximab studies [46]; a difference potentially due to the sparse data situation.

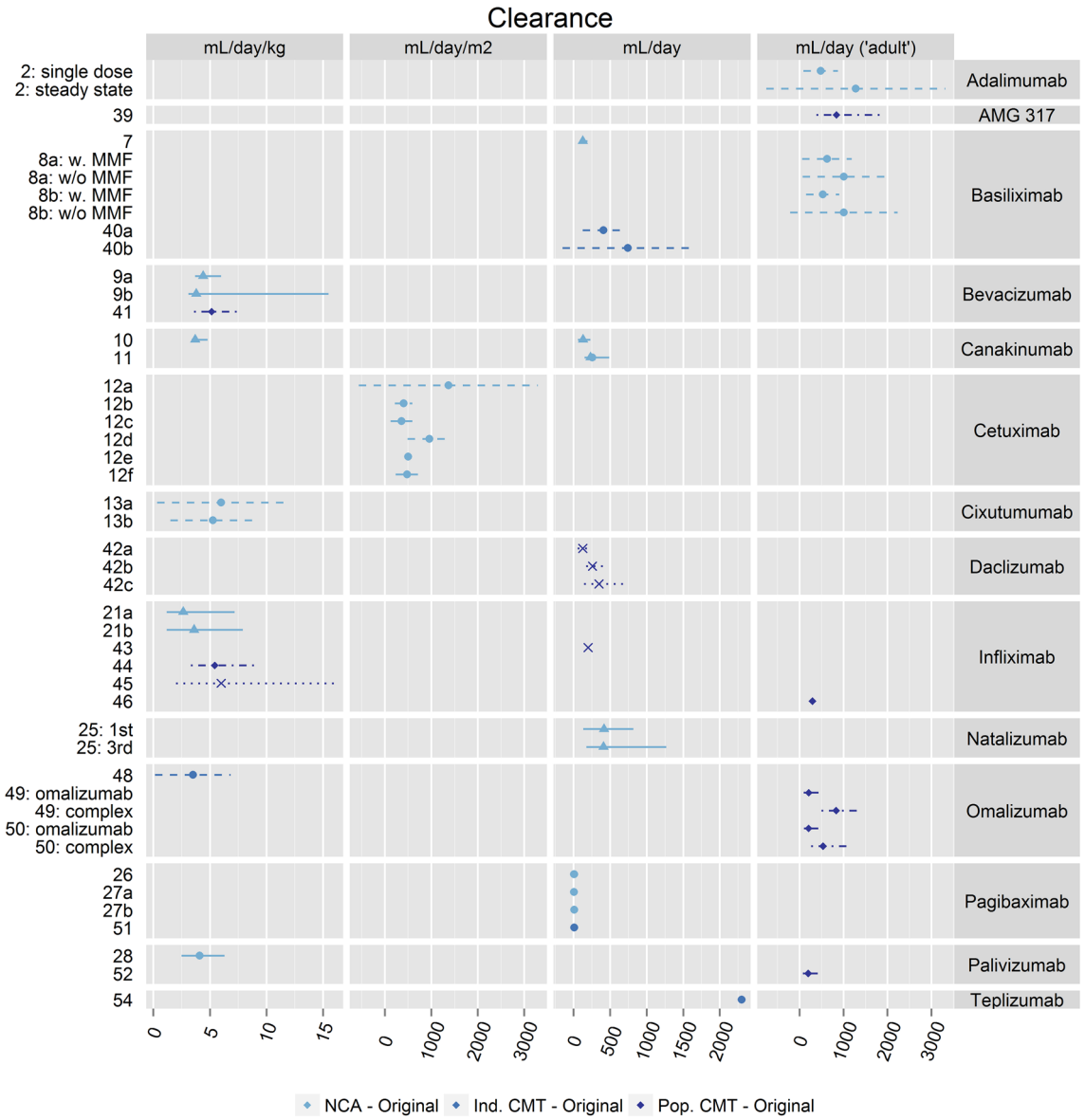

Fig. 3 Estimate and variability between individuals of CL values (*x*-axis) within and across monoclonal antibodies. The *numbers* on the *y*-axis refer to the number assigned in the 'Study no.' column of Tables 3 and 5. First panel: CL in mL/day/kg; second panel: CL in mL/day/m^2; third panel: CL in mL/day (non-scaled value); fourth panel: CL in mL/day (scaled to 'reference adult'). The different *colours* show the type of pharmacokinetic analysis. No transformation based on body weight was performed on CL values; hence, they are referred to as 'original' (see explanation in Sect. 4.3.3). *Points* indicate the mean, *dashed lines* indicate the 95 % CI calculated based on reported standard deviation and the mean, *triangles* indicate the median, *solid lines* indicate the range, *diamonds* indicate the estimate for typical individual (Pop. CMT), *dot-dashed lines* indicate the 95 % CI calculated based on reported between subject variability, *crosses* indicate the mean or median EBEs (Pop. CMT) and *dotted lines* indicate the range of EBEs. *CI* confidence interval, *CL* clearance, *EBEs* empirical Bayes estimates, *Ind. CMT* individual compartmental analyses, *MMF* mycophenolate mofetil, *NCA* non-compartmental analyses, *Pop. CMT* population compartmental analysis, *w* with, *w/o* without

A large diversity in the pharmacokinetic analysis approaches and reported parameter units was observed, which complicated comparison of V_d values across studies, as well as their comparison with reports in adults. The comparison was further challenged by the fact that some studies reporting a two-compartment model did not report the estimate for the peripheral volume. As a first approach to enable comparison between NCA and Ind./Pop. CMT parameters, the central (V_1) and peripheral (V_2) volumes were summed to a total volume (V_{tot}) for studies in which both were reported. In the next step, the reported parameters were transformed as follows:

- for V_d reported in volume (mL, L) for the studied population, the mean/median estimate was normalised by the reported mean/median BW (for studies in which both were reported) and then scaled linearly to 70 kg ('reference adult');
- for V_d reported in volume/kg BW (e.g. mL/kg), the estimate was scaled linearly to 70 kg;
- for V_d reported in volume/BSA (e.g. L/m^2), the estimate was scaled linearly to 1.73 m^2 (also considered 'reference adult'); and
- V_d reported in values scaled to a reference adult (70 or 80 kg) were left untransformed.

A graphical overview of the original and transformed V_d values for the different mAbs is provided in Fig. 2. The conjugated mAb gemtuzumab ozogamicin showed rather atypical parameter values compared with the other mAbs, potentially due to its different structural nature, and was therefore excluded from the summary. V_d/V_{tot} was reported in a total of 25 studies of 14 different mAbs (12 NCAs, 13 Ind./Pop. CMTs). By excluding studies not reporting BW, 19 studies were retained (9 NCA, 10 Ind./Pop. CMT). In some cases, parameters were reported for several groups within one study (e.g. based on dose or age); all groups were considered. The median (range) of V_d/V_{tot} scaled to a reference adult was 6,310 (3,220–19,900) mL ($n_{groups} = 32$) (Fig. 2, right panel), in agreement with physiological ECF and plasma volume values. In adults, median (range) estimates of V_1 and V_2 have been reported to be 3,100 (2,400–5,500) mL and 2,800 (1,300–6,800) mL, respectively [3]; which would give a comparable V_{tot} of 5,900 (3,700–12,300) mL, suggesting that V_d/V_{tot} scales reasonably well with BW. Regarding V_d/V_{tot} and *age*, no trend could be observed; the highest V_d was observed for pagibaximab in pre-term neonates [63, 85] but a value in the lower range (3,710 mL; scaled value) was observed for infliximab in Kawasaki disease (<1 year) [23], indicating that a large variability can be expected.

Eight studies identified factors (covariates) influencing V_d, related to population characteristics (e.g. BW, ethnicity) or the investigated drug (e.g. formulation strength, administration route). As in adults [3], BW was most frequently identified, being significant in all studies performing covariate analysis [41, 42, 50, 58, 60, 116–118]. Two studies, both covering a wide age range, included an age effect on top of BW [59, 60], indicating that there might be maturation processes that need to be considered. In summary, V_d seems to scale reasonably well with BW. Nevertheless, the variability in the reviewed studies was high, which indicates that the relation to body size should be explored further before it is considered as a factor in dosing regimens.

Seven studies reported an estimate of inter-compartmental clearance (Q) or transfer rate constants [transfer rate constant (first-order) from the central (1) to peripheral (2) compartment (k_{12})/from the peripheral (2) to central (1) compartment (k_{21})]. To enable comparison, k_{12}/k_{21} were transformed to Q (e.g. $Q = k_{12} \cdot V_1$); no transformation based on BW was performed for this parameter (see discussion in Sect. 4.3.3). The median (range) of Q reported as a BW-normalised value was 14.6 (3.52–334) mL/day/kg ($n_{groups} = 6$). One study reported a Q value allometrically scaled to 70 kg (879 mL/day) [42]. Finally, unscaled estimates of Q were reported for three studies: 72 [119], 148 [118] and 658 mL/day [116]. Given this sparse and heterogeneously reported data, it is difficult to infer whether these results are in total comparable with adult values [median (range): 789 (154–53,300) mL/day) [3]].

4.3 Elimination

4.3.1 General Principles and Mechanisms

Due to the physicochemical properties of mAbs, elimination mechanisms that are of main importance for small molecules, such as hepatic enzymatic metabolism and renal excretion, are of minor importance. The elimination of mAbs is instead considered to comprise two pathways: one IgG non-specific and one target-mediated pathway [8]. The non-specific pathway refers to intra-cellular proteolysis, equivalent to the degradation of endogenous IgG. This pathway is highly influenced by the FcRn, which binds to IgGs (endogenous as well as mAbs), directing them from the intracellular space back to the blood or ECF and, thus, protecting them from degradation. The FcRn is, hence, responsible for the long half-life of IgG molecules [47]. The vascular endothelial cells or reticuloendothelial system seem to be the main site for FcRn salvage, but FcRn is also expressed in other cells [47]. The FcRn salvage pathway is usually not saturated in the therapeutic concentration ranges and/or by physiological variations of endogenous IgG [3, 8]. The affinity between FcRn and the (Fc part of) IgG is species specific; the lower affinity of human FcRn and mouse/rat-derived mAbs typically results in a shorter half-life for these mAbs. The second, target-mediated pathway (often saturable) refers to the degradation mAbs may undergo after binding to their specific target(s), commonly resulting in a faster CL of the mAb-target complex than the unbound mAb. The increased elimination rate may be caused by either direct internalisation of the drug-target complex (for mAbs with membrane-bound targets) or internalisation upon binding to FcγRs, which are expressed by various cells of the immune system. To what extent this pathway affects the total CL depends on aspects such as target localisation (important for mAbs with a membrane-bound, internalising target), target expression and binding affinity [3, 48].

Other disease-specific (non-target-mediated) attributes might also affect the elimination of mAbs. In inflammatory bowel diseases, for example, a low serum albumin concentration has been found to predict higher CL [49, 50]. This relationship might be explained by a general protein loss in the damaged 'leaky' gut [51, 52]. Similarly, a relationship between protein loss and CL has been identified in patients with proteinuria [53], suggesting that, for example, albumin acts as a surrogate marker of this additional 'CL route' in these diseases.

4.3.2 Developmental Aspects

The impact of growth and maturation on the elimination pathways has not been well-characterised. For small molecules, maturation of metabolic enzymes (e.g. the cytochrome P450 system) and kidney function are known aspects influencing pharmacokinetics in children [11]. Use of age (e.g. gestational or post-natal) has been suggested to account for these processes, as a surrogate marker of maturation [32, 54]. Since mAbs neither undergo renal excretion nor classical hepatic enzymatic metabolism to a notable extent, these principles may not be directly transferrable to this drug class. There might, however, be other maturation processes that need to be considered. Indeed, Robbie et al. described a maturation process of palivizumab CL related to post-menstrual age (PMA) [42] (further discussed below); however, the cause of this maturation was not described. Factors affecting concentrations of endogenous IgG might provide some hints, given the molecular similarity. At birth, the concentrations of all IgG isotypes are low as a result of an impaired IgG production [55]. IgG_1 concentrations stabilise by the age of 5 years, whereas other subclasses may not reach adult levels until adolescence [56]. Low IgG concentrations during childhood could also be a result of increased catabolism or excretion. This is, however, most frequently observed in certain diseases [57].

To our knowledge there is no information regarding the development (expression, efficacy, IgG affinity, etc.) of the FcRn in the various cell types in children compared with in adults and how these potential differences could affect CL of mAbs. As mentioned above, mAb CL can also be affected by disease-specific factors (target expression/availability or non-target related). If the disease progression/state differs between children and adults this may translate into differences in CL. In conclusion, the influence and clinical implication of maturation processes on mAb CL is still unclear and needs further investigation.

4.3.3 Summary of Clearance-Related Parameters

The median (range) terminal half-life was 11.9 (3.85–29.7) days ($n_{studies} = 23$, $n_{groups} = 34$). In general, a large variability between individuals was seen; palivizumab showed the most extreme example with a median (range) of 22.4 (9.9–56.7) days [86]. The variability was too large to evaluate differences considering the genetic origin of mAbs, as inferred in adults; the ranges of central measure were 4.8–29, 3.85–24.4 and 6.63–23.7 days for chimeric, humanised and fully human mAbs, respectively.

Similar to the situation for V_d, a large diversity concerning analysis approaches and reported parameter units was observed for CL. In order to harmonise the units of CL values, strong assumptions would be required with respect to both scaling approaches and handling of missing information, making across-study comparisons of CL unfeasible (this also applies for Q). Hence, unlike for V_d, no parameter transformation was performed and the estimates were summarised with respect to their reported units. After excluding two studies that reported implausible units (see Table 4) and the conjugated mAb gemtuzumab ozogamicin due to its different nature, CL values from a total of 27 studies of 14 different mAbs were available (Fig. 3). Some studies reported CL for several groups; all groups were included in the following summary [presented as median (range)]; note that one of the studies reported two of the options:

- Eleven studies reported CL in volume/time for the studied population: 199 (7.68–2,300) mL/day ($n_{groups} = 16$, Fig. 3, panel 3);
- Nine studies reported a BW-normalised CL: 4.25 (2.64–6.00) mL/day/kg ($n_{groups} = 12$, Fig. 3, panel 1);
- One study reported a BSA-normalised CL: 492 (360–1,370) mL/day/m^2 ($n_{groups} = 6$, Fig. 3, panel 2); and
- Seven studies reported CL in volume/time scaled to a 'reference adult': 528 (198–1,280) mL/day ($n_{groups} = 13$, Fig. 3, panel 4):
  - Six of these scaled to a BW of 70 or 80 kg (three used a power model with an exponent of 0.75, two estimated the exponent being close to 1, and one did not report the used covariate model); and
  - One of them scaled linearly to a BSA of 1.73 m^2.

The estimates scaled to a reference adult covered the range of linear CL pathway for adults (200–500 mL/day) reported in Dirks and Meibohm [3], predominantly showing values in the upper range or higher. This result is not particularly surprising since the CL reported for children in this review typically represents the total CL, without differentiation of potential linear and non-linear elimination pathways, whereas CL of mAbs in adults frequently is shown to also have a non-linear/dose-dependent part [3], resulting in a higher total CL. When looking at total CL of molecules with saturable CL mechanisms, a non-linear

elimination pathway relating to target availability will be observed at saturation. At lower concentrations, a mixture of both linear and non-linear elimination will occur. Which pathway will dominate will depend on the closeness to saturation. The fact that only total CL typically has been estimated in children might partially explain the different covariate models used to scale CL with BW (i.e. linear scaling, exponent of power function, etc.).

In fact, a trend towards dose dependency in the pharmacokinetics could be observed in children when several dose concentrations were available in one study (e.g. for cetuximab) [93]. However, of the 54 reviewed studies, only three reported non-linear and/or target-mediated elimination [41, 58, 116]. These studies benefited from the use of a population analysis approach on pooled clinical trial data from children and adults. The limited number of identified non-linear CL processes in the paediatric studies may arise from (i) true exclusively linear elimination process(es); (ii) the studied dose range not being wide enough; (iii) complexity of the pharmacokinetic analysis; (iv) a sparse data situation; (v) a small number of individuals; or (vi) non-linearity not being considered during model development. Further research is urgently needed to better characterise CL mechanisms in children, including characterisation of target availability in case of saturable elimination pathways, and how to more adequately scale the pathways from adults to children in these more complex relationships.

Characteristics identified as relating to CL include (i) patient-specific characteristics (e.g. BW, age or ethnicity); (ii) factors related to disease and/or disease status (e.g. chronic lung disease, albumin concentration); and (iii) anti-drug antibodies (ADAs; further discussed in Sect. 6). As for V_d, BW was the most frequently introduced covariate, included in all but three of the studies performing covariate analysis ($n_{studies} = 12$) [41, 42, 50, 58, 116–120]. Two of these three studies, however, reported CL for two age groups or a CL corrected by base metabolism rate (both known to correlate with BW) [59, 60]. As mentioned, BW was introduced in three of the models using a power function with an exponent of 0.75 [42, 70, 116], in agreement with allometric principles [31]. In two studies, the exponent was instead estimated to approximately 1 [41, 58], i.e. a linear model. Similarly, nine studies reported a BW-normalised CL, which is also a linear scaling model [23, 50, 59, 79, 86, 92, 94, 117, 121]. The different BW scaling models may be related to a sparse data situation, not accounting for non-linear/target-mediated pathways (see above), as well as not taking maturation processes into consideration. Robbie et al. [42] described a maturation process of palivizumab CL related to PMA, after adjusting for BW. A lower CL was estimated for younger children but the cause of this effect was not described.

Factors related to disease and/or disease state have been identified for the paediatric population, similarly to adults. This indicates that target-mediated elimination processes may play an important role for mAb CL also in the paediatric population and, hence, need to be considered more frequently.

To summarise, the elimination of mAbs is complex and may depend on body size, maturation processes and target expression/availability (pharmacodynamics), which may result in non-linear mAb CL. However, based on the limited and diversely reported data, conclusions regarding the impact of these factors on CL in the paediatric population are as yet precluded: more knowledge could have been gained if a population approach had been performed more frequently, since it allows for combined analysis of data across doses and ages (including prior knowledge). As mentioned, mAb pharmacokinetics and pharmacodynamics are inter-related and would benefit from simultaneous consideration—this can only be achieved with more sophisticated models and approaches.

5 Pharmacodynamics

The goal of any drug therapy is to translate into clinical benefit. Thus, a key aspect during drug research and development should be not only to adequately characterise the pharmacokinetics of the drug but also to establish the relationship between drug exposure and clinical response. Ideally, this relationship will be used further to design optimal dosing regimen and, hence, increase the probability of clinical success. In this section, pharmacokinetic–pharmacodynamic characteristics of studies already reviewed are systematically extracted (Table 7). To allow for a better interpretation and comprehension of the results, mAb targets and their localisation are also provided along with the clinical domain, indication, reported biomarkers and/or clinical outcome. Since the ultimate objective of this compilation was to summarise and critically evaluate pharmacokinetic–pharmacodynamic relationships, additional studies providing only safety and/or efficacy data were not considered.

Pharmacodynamic characteristics were available for 18 mAbs in 38 of the evaluated studies. The main clinical domains were immunology, oncology and infectious diseases, consistent with mAbs currently approved or in development (Fig. 4).

5.1 Target Types and Pharmacodynamic Measures/Biomarkers

Depending on the type of target and its localisation, the mAb mechanism of action may differ. Upon cell binding,

Table 7 Pharmacodynamic and pharmacokinetic/pharmacodynamic characteristics of monoclonal antibodies with reported pharmacokinetic analysis

Target	Target localisation and type	Clinical domain	Indication	PD measures (biomarkers/clinical outcomes)[a]	PD and/or PK/PD findings[b]	Refs.
Adalimumab						
TNF-α	Soluble and membrane-bound cytokine	Immunology	Crohn's disease	CDAI, corticoids/immune-modulator discontinuation, CRP concentration, 'height velocity'(=growth rate), number of fistulae, PCDAI	PK/PD Tendency towards higher clinical response (PCDAI) and fistulae remission for the higher dose. No differences observed for the other reported PD measures Remission and response rates significantly higher for drug-naive patients	[89]
			Focal segmental glomerulosclerosis	GFRe, serum albumin concentration, urine protein:creatinine ratio	PK/PD Increased GFRe and serum albumin concentrations, as well as decreased urine protein:creatinine ratio found if C_{min} >4 μg/mL (target concentration in rheumatoid arthritis for adults) Significant correlations observed between (i) urine protein:creatinine ratio; or (ii) serum albumin and $t_{½}$ of adalimumab. Urine protein:creatinine ratio suggested as a novel approach for dose adjustments of adalimumab in nephrotic patients	[90]
			Polyarticular juvenile idiopathic arthritis	ACR Pedi response criteria	PD Disease flares decreased and ACR Pedi response improved in patients receiving adalimumab PK/PD Tendency towards higher ACR Pedi response among patients receiving concomitant methotrexate observed	[87, 88, 91]
Alemtuzumab						
CD52	Membrane-bound glycoprotein	Oncology	Acute lymphoblastic leukaemia	Bone marrow blast count and circulating blast status	PD Apparent limited efficacy for the treatment of children with relapsed acute lymphoblastic leukaemia reported PK/PD PK/PD relationship not evaluated	[77]
AMG 317						
IL-4Rα	Membrane-bound receptor	Immunology	Asthma	IgE concentration	PD No PD measures reported in the paediatric subpopulation PK/PD In adults, a higher 'IgE concentration reduction from baseline' achieved with higher cumulative *AUC*	[116]

Table 7 continued

Target	Target localisation and type	Clinical domain	Indication	PD measures (biomarkers/ clinical outcomes)[a]	PD and/or PK/PD findings[b]	Refs.
Basiliximab						
IL-2Rα/CD25	Soluble and membrane-bound receptor	Immunology	Renal transplant rejection	Duration of CD25 blockage, duration of $CD25^+$ T cell suppression, % total and blocked $CD25^+$ T cells, sIL-2R temporal profiles	PK/PD CD25 blockage significantly related with *AUC*, but not with C_{max} Duration of CD25 saturation significantly related with time of basiliximab concentration >0.1 μg/mL (threshold previously observed in adults) mAb concentrations >0.2 μg/mL generated suppression (<3 %) of $CD25^+$ T lymphocytes in the peripheral blood Unclear relationship between CD25 saturation/$CD25^+$ T cell suppression and acute rejection reported	[60, 65]
Bevacizumab						
VEGF-A	Soluble glycoprotein	Oncology	Solid tumours	Bone age, circulating endothelial cells, fibroblast growth, ovarian function, paediatric limb length discrepancy, RECIST, thrombospondin-1, VEGF	PD Exploratory analysis on circulating endothelial mobilisation and viability consistent with data available in adults PK/PD No relationship observed between (i) baseline VEGF; (ii) thrombospondin-1; (iii) fibroblast growth; (iv) circulating endothelial cells; or (v) progenitor subset, and clinical benefit	[92]
Canakinumab						
IL-1β	Soluble cytokine	Immunology	Cryopyrin-associated periodic syndromes	Arthralgia, myalgia, conjunctivitis, fatigue or malaise, CRP concentration, headache or migraine, PGA, SAA concentration, urticarial rash	PD Complete clinical and biochemical response achieved within 7 days after the first dose in all patients. If relapse, response rapidly re-induced with additional treatment in most patients Reduction of inflammatory marker (CRP and SAA) concentrations shown after single dose PK/PD PK/PD relationship not established	[78, 79]
			Systemic juvenile idiopathic arthritis	ACR Pedi response criteria (including number of joints with active arthritis, CRP concentration, functional ability, fever), ESR, median time to relapse	PK/PD 2 μg/mL identified as critical systemic threshold to obtain an acceptable low probability of flares using a PK/flare model (model not reported) 4 mg/kg q4w (subcutaneous), close to 'saturation of response', proposed to maintain mAb above this threshold (simulation)	[80, 81]

Table 7 continued

Target	Target localisation and type	Clinical domain	Indication	PD measures (biomarkers/ clinical outcomes)[a]	PD and/or PK/PD findings[b]	Refs.
Cetuximab						
EGFR	Membrane-bound receptor	Oncology	Advanced refractory solid tumours	EGFR, immunohistochemistry, RECIST, sequence mutations in EGFR or K-RAS	PD Stable disease achieved in 18 patients (38.5 %) PK/PD No apparent relationship between response and any biomarker	[93]
Cixutumumab						
IGF-IR	Membrane-bound receptor	Oncology	Refractory solid tumours and Ewing sarcoma	Change in peripheral blood mononuclear cells, serum IGF-I, IGF-II, IGFBP-2, and IGFBP-3 concentrations	PD None of the patients with refractory solid tumours showed complete or partial response, 3 patients with Ewing sarcoma had confirmed partial responses PK/PD IGF-I concentrations consistently increased after 1 dose No relationship between response and tumour expression of IGF-I, IGF-II or IGF-IR apparent	[94]
Daclizumab						
IL-2Rα/CD25	Soluble and membrane-bound receptor	Immunology	Prophylaxis of acute renal transplant rejection	Biopsy-proven or presumptive acute rejection episode, IL-2R saturation on peripheral blood lymphocytes, rate of ADA development	PK/PD Dose of 1 mg/mL provided average C_{min} values within the range previously described sufficient to achieve complete saturation of IL-2R in adults; however, inadequate blockade observed in this population PK/PD relationship not evaluated	[118]
Eculizumab						
C5	Soluble protein	Haematology/ immunology	Atypical haemolytic uraemic syndrome	Complement activity, health-related QoL, haematological normalisation, plasma exchange, need of new dialysis, renal function parameters (GFR, CL_{CR})	PD Significant improvement in all PD measures PK/PD PK/PD relationship not evaluated	[95]

Table 7 continued

Target	Target localisation and type	Clinical domain	Indication	PD measures (biomarkers/ clinical outcomes)[a]	PD and/or PK/PD findings[b]	Refs.
Infliximab						
TNF-α	Soluble and membrane-bound cytokine	Immunology	Crohn's disease	CDAI, blood inflammatory markers (ESR, CRP concentration), FC concentration, loss of response defined by HBI, PCDAI, PGA, TNF-α concentration and activity	PK/PD Unclear relationship between drug concentration and response, although higher responses observed in groups with higher dose or shorter dosing intervals Lower biological activity of TNF-α reported after infliximab, although positive relationship found between infliximab and TNF-α concentrations. Higher infliximab concentrations associated with lower FC concentrations during induction, but not at later times. No relationship with blood inflammatory markers found FC concentration did not appear to relate to improved outcome	[82, 83, 97–100]
			Juvenile idiopathic arthritis	ACR Pedi response criteria, JIA core set	PD No significant difference between placebo and dose groups reported, although higher percentage of responders (ACR Pedi 30) obtained with infliximab treatment PK/PD No difference in response between dose groups. However, higher C_{min} pointed towards increase in proportion of patients with improvement	[59, 101]
			Kawasaki disease	Echocardiograms and body temperature	PK/PD PK/PD relationship not evaluated	[23]
			Ulcerative colitis	Blood inflammatory markers (ESR, CRP concentration), FC concentration, Mayo score, PUCAI	PK/PD Higher infliximab concentrations at week 8 associated with higher clinical response; maximal effect associated with infliximab concentration >40 μg/mL. Steady-state concentrations at week 30 positively related with improvement in PUCAI Higher infliximab concentrations associated with lower FC levels during induction, but not during the maintenance phase. No correlation with blood inflammatory markers found Relationship between clinical outcome and FC not evaluated	[13, 98]

Table 7 continued

Target	Target localisation and type	Clinical domain	Indication	PD measures (biomarkers/ clinical outcomes)[a]	PD and/or PK/PD findings[b]	Refs.
Natalizumab						
Integrin α4	Membrane-bound cell adhesion protein	Immunology	Crohn's disease	Absolute number of circulating lymphocytes, CRP concentration, integrin α4 receptor saturation, PCDAI, QoL, serum albumin concentration	PD PCDAI scores significantly decreased although QoL remained similar. No significant changes observed in CRP or serum albumin concentrations PK/PD Maximum integrin receptor saturation (>90 %) observed at first sampling point (2 h post-infusion), and then decreased over time	[103, 104]
Omalizumab						
IgE	Soluble immunoglobulin	Immunology	Allergic asthma	Asthma symptoms score, free and total IgE concentration, morning peak expiratory flow, use of rescue medicines (bronchodilators)	PK/PD PK/PD model relating omalizumab concentrations to free and total IgE concentration developed: omalizumab suppressed free IgE concentrations in a non-linear dose-, and baseline IgE-dependent manner; positive feedback mechanism of free IgE on the IgE production identified, suggesting that 5 years would be needed to recover IgE baseline values and about 15 years to return to initial baseline IgE production upon treatment withdrawal Free IgE suppression identified to translate well into clinical outcome; a target IgE concentration of 14 ng/mL established, achieving the maximum clinical effect A dosing table taking BW and baseline IgE into account suggested based on the PK/PD model	[41, 58, 121]
Pagibaximab						
Staphylococcal lipoteichoic acid	*Staphylococcus* membrane	Infectious diseases	Prevention of Staphylococcal sepsis	Bronchopulmonary dysplasia, death, NEC, opsonophagocitic activity (bacterial killing), retinopathy of prematurity requiring surgery, severe intraventricular haemorrhage	PD Clinical studies have shown limited clinical efficacy PK/PD Drug concentration >500 μg/mL associated with Staphylococcal sepsis prevention in vitro and in vivo Pagibaximab shown to enhance opsonophagocitic activity in serum. However, no dose-dependent clinical effect observed in studied dose interval (30–90 mg/kg) A new dosing regimen of 100 mg/kg daily for 3 days and weekly for 3 weeks proposed to maintain drug concentrations >500 μg/mL based on established PK model	[63, 64, 85]

Table 7 continued

Target	Target localisation and type	Clinical domain	Indication	PD measures (biomarkers/ clinical outcomes)[a]	PD and/or PK/PD findings[b]	Refs.
Palivizumab						
RSV glycoprotein F	Virus	Infectious diseases	RSV infection (prophylaxis)	Days of hospitalisation, hospital days with supplemental O_2 therapy, LRI	PD After single dose, no significant differences observed between placebo and treatment groups. However, multiple doses of 15 mg/kg decreased the number of positive cultures and RSV detection Both 10 and 15 mg/kg decreased the number of hospitalisations due to RSV infection PK/PD 3–5 monthly injections resulted in C_{min} >40 μg/mL (concentration associated to anti-RSV activity in rats)	[42, 86, 105–107]
Rituximab						
CD20	Membrane-bound B cell receptor	Haematology, oncology and immunology	Immune thrombocytopenic purpura, or Evans syndrome	B cell depletion, IgM and IgG concentration, bleeding severity (for ITP), platelet count	PD 375 mg/m^2 q1w for 4 weeks induced complete cell depletion in all patients for ≥12 weeks Sustained platelet count observed in 31 % of patients during 4 consecutive weeks, being weakly associated to Evans syndrome, female and Black ethnic group PK/PD PK/PD relationship not evaluated	[122]
			Steroid-dependent nephrotic syndrome	B cell depletion, frequency of relapses per 6 months, IgG, IgA and IgM concentration, probability of relapse-free survival, steroid dose or free period	PD Complete cell depletion observed in 88 % of patients after single dose of 375 mg/m^2 Relapse observed in 9/12 (75 %) at median time of 129 days. Most of the relapses occurred simultaneously with B cell recovery (50 % survival time of 119 days) Trend towards higher decrease in IgM concentrations observed in responders after rituximab therapy. IgM suggested as surrogate marker of clinical response	[110]
Teplizumab						
CD3	Membrane bound T cell receptor	Immunology	Type 1 diabetes mellitus	Change from baseline in *AUC* for peptide C, HbA_{1c}, insulin use, number of circulating $CD4^+$ and $CD8^+$ T cells	PD No significant differences in clinical outcome when comparing dosing groups and placebo PK/PD PK/PD relationship not evaluated	[123, 124]

Table 7 continued

Target	Target localisation and type	Clinical domain	Indication	PD measures (biomarkers/ clinical outcomes)[a]	PD and/or PK/PD findings[b]	Refs.
Tocilizumab						
IL-6R	Soluble and membrane-bound receptor	Immunology and oncology	Polyarticular juvenile idiopathic arthritis	ACR Pedi response criteria, ESR	PD Significantly higher ACR Pedi responses after therapy than after placebo PK/PD Lower drug exposure resulted in lower clinical efficacy Comparable responses observed in the 10 mg/kg for <30 kg and the 8 mg/kg for >30 kg groups	[28, 111]
			Systemic juvenile idiopathic arthritis	ACR Pedi response criteria, JIA score set (including ESR, CRP concentration) neutrophil count, sIL-6, white blood cell count	PD Sustained clinical response observed more frequently with therapy than with placebo PK/PD Apparent increase of response duration with increasing doses observed Dose related increases of IL-6 and IL-6R concentration, both in magnitude and duration. ESR and CRP concentrations decreased after drug administration reaching minimum concentrations 1–2 weeks after 1 dose No clear trend between mAb exposure ($AUC_{2\ weeks}$, C_{min} and C_{max}) and response (ACR Pedi response criteria) reported	[13, 112–115]

Pharmacodynamic findings comprise biomarker and clinical outcome (not safety) with respect to monoclonal antibody dose/dosing; for pharmacokinetic/pharmacodynamic findings, relationships between (i) pharmacokinetic—clinical outcome, (ii) pharmacokinetic—biomarker and (iii) biomarker—clinical outcome are separately summarised (typically not all three types were available)

ACR Pedi American College of Rheumatology pediatric criteria, *ADA* anti-drug antibody, *AUC* area under the plasma concentration–time curve, $AUC_{2\ weeks}$ AUC from time zero to 2 weeks, *BW* body weight, *C5* complement component 5, *CDx* cluster of differentiation x, *CDAI* Crohn's Disease Activity Index, CL_{CR} creatinine clearance, C_{max} maximum concentration, C_{min} minimum concentration, *CRP* C-reactive protein, *EGFR* epidermal growth factor receptor, *ESR* erythrocyte sedimentation rate, *FC* faecal calprotectin, *GFRe* estimated glomerular filtration rate, HbA_{1c} glycated haemoglobin, *HBI* Harvey Bradshaw Index, *Ig* immunoglobulin, *IGF* serum insulin-like growth factor, *IGF-xR* IGF-*x* receptor, *IGFBP* IGF binding protein, *IL* interleukin. *IL-xR* IL-*x* receptor, *ITP* immune thrombocytopenic purpura, *JIA* juvenile idiopathic arthritis, *K-RAS* Kirsten rat sarcoma viral oncogene homologue, *LRI* low respiratory illness/infection, *mAb* monoclonal antibody, *NEC* necrotising enterocolitis, *PCDAI* Paediatric Crohn's Disease Activity Index, *PD* pharmacodynamic, *PGA* Physician Global Assessment, *PK* pharmacokinetic, *PUCAI* Paediatric Ulcerative Colitis Activity Index, *QoL* quality of life, *qxw* every *x* weeks, *RECIST* response evaluation criteria in solid tumours, *Refs.* references, *RSV* respiratory syncytial virus, *SAA* serum amyloid A protein, *sIL-xR* soluble IL-*x* receptor, $t_{½}$ half-life, *TNF-α* tumour necrosis factor-α, *VEGF* vascular endothelial growth factor

[a] PD measures presented in alphabetical order

[b] Dose-response relationships included

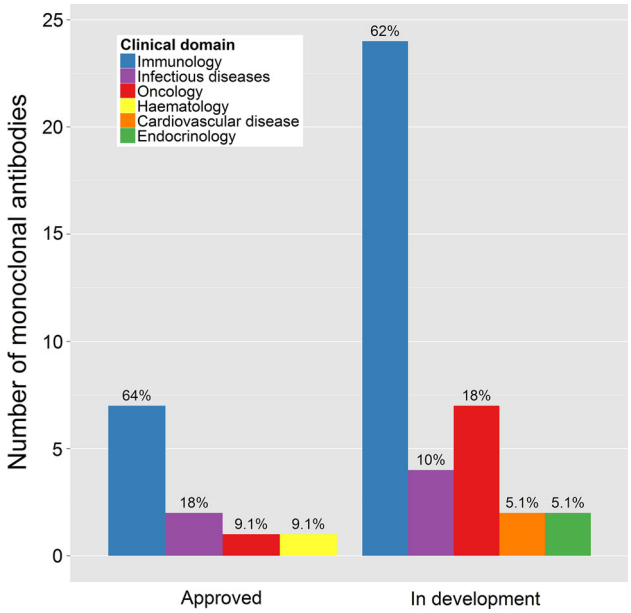

Fig. 4 Number of mAbs in different clinical domains (April 2014): approved mAbs (*left*) and mAbs in development (*right*). The *number above each bar* corresponds to the percentage of mAbs in the clinical domain within the approved or in development groups. *mAbs* monoclonal antibodies

mAbs can trigger lytic or coating effects, resulting in either lysis/apoptosis (e.g. rituximab) or activation/inhibition of the receptors' biological functions (e.g. daclizumab). For soluble targets, mAbs reduce the free target concentration, and thereby decrease the target activity and/or increase target elimination [8] (e.g. omalizumab). Generally, a good agreement of reported pharmacodynamic measures (biomarkers and/or clinical outcomes) was seen within indications. In some cases, drug-specific markers/targets were also characterised, such as tumour necrosis factor-α for adalimumab or integrin α4 for natalizumab. Nevertheless, a diverse range of pharmacodynamic measures was evaluated in the different studies, as can be observed in Table 7, indicating the complexity of these diseases from a clinical point of view and a current lack of validated biomarkers. Biomarkers are biological molecules that should (i) be minimally invasive and easy to obtain; (ii) be sensitive to the drug treatment; and (iii) relate to the state/progression of the disease. Hence, biomarkers could act as a link between drug exposure and ultimate clinical response to allow for an early assessment of the pharmacological response [61]. Asthma is one of the few examples in this review for which a validated biomarker (IgE) exhibiting all mentioned properties was identified; a complex task in these clinical domains.

5.2 Pharmacokinetic–Pharmacodynamic Findings

Although 72 % of the pharmacokinetic studies also reported pharmacodynamic measures, few were able to establish significant relationships between dose/exposure and response. As previously mentioned, these results could be due to a low number of individuals/samples, the disease complexity and the high variability deduced from these aspects. Most frequently, authors were only able to conclude a trend towards clinical benefit. When looking at the type of performed pharmacokinetic analysis (in the pharmacodynamic subset), most reported an NCA or EDCA (82 %). Only seven studies (18 %) characterised the temporal concentration profiles of the drug.

Another aspect to consider is the mutual influence of pharmacokinetics and pharmacodynamics; mAbs are designed to trigger pharmacological response upon binding to their target, which might in return impact the pharmacokinetics (see Sect. 4.3.1) [62]. Simultaneous analyses of mAb concentrations and pharmacodynamic markers (target concentration/biomarkers/clinical outcome) are, thus, advantageous to fully understand the response. Given the situation, distinguished studies are discussed in the following section.

5.2.1 *mAb Examples*

Pagibaximab binds the lipoteichoic acid, a highly conserved macromolecule needed for staphylococcal survival. A dose-escalation study was undertaken in neonates, showing a dose-dependent antibacterial activity over the studied range (10–90 mg), which only translated into a clinical response in the highest dose group [63]. Evaluation of measured drug concentrations revealed that mAb concentrations >500 μg/mL (threshold established from in vitro studies) were not achieved in many patients. A pharmacokinetic model was developed a posteriori to optimise the dosing regimens based on the identified threshold [64]. However, in order to establish an adequate individualised dosing regimen, considering, for example, time above the threshold, the authors would also need to characterise the link between the continuous biomarker (opsonophagocytic activity) and the dichotomous clinical response. This important step towards individualised therapy has, to our knowledge, not been performed.

Basiliximab, used to prevent renal transplant rejection, is another mAb that could benefit from an exposure–response modelling approach. A significant relationship has been established between basiliximab exposure (*AUC*) and the suppression of interleukin-2Rα and $CD25^+$ T lymphocytes. However, similarly to pagibaximab, no distinct relationship between biomarkers and clinical outcome has been characterised [65, 66]. Use of a population approach might enable characterisation of the relationship between basiliximab concentrations over time and

suppression of, for example, $CD25^+$ T lymphocytes, which could be used to improve dosing regimens and, thus, increase the probability of clinical benefit.

Omalizumab represents the only example for which a pharmacokinetic–pharmacodynamic model has been developed in children. Utilising a target-mediated drug disposition (TMDD) model, temporal concentration profiles of unbound and complex-bound omalizumab as well as IgE (i.e. target) were characterised [58]. In addition, a non-linear link between free IgE and response was identified (no specific differentiation was mentioned between adults and children). A target IgE suppression concentration of 14 ng/mL was suggested to achieve maximum clinical effect. In a subsequent analysis of long-term data, a feedback control mechanism of IgE on IgE production was identified [41]. Simulations, based on the TMDD model, showed that IgE concentrations could be used to guide treatment decisions. Indeed, the approved dosing regimen of omalizumab is based on IgE concentration and BW. The simulations also suggested that the therapy could be temporarily paused when IgE concentrations are low, due to the disease-modifying effect of omalizumab (reduced IgE production rate).

5.2.2 Developmental Aspects

Several studies analysing pharmacokinetics and pharmacodynamics in children aimed for the therapeutic plasma concentration established for adults (e.g. basiliximab). This assumption implies that the pharmacodynamic characteristics are the same in the two populations, which might not always be the case [12, 25]. Reasons for discrepancies between adult and paediatric patients could potentially arise from differences in target concentration/expression/availability or binding affinity, resulting from differences in disease activity and/or maturation processes. Accounting for pharmacodynamic maturation processes could in principle also explain discrepancies seen in the pharmacokinetics, given their mutual influence. However, none of the reviewed studies considered that pharmacodynamics may differ between these two patient populations. More research in this area is needed before drawing conclusions on pharmacodynamic differences across ages.

6 Immunogenicity

6.1 General Principles and Mechanisms

Although mAbs and other therapeutic proteins generally are considered rather safe and non-toxic, repeated administration often leads to generation of ADAs [67–69]—also referred to as immunogenicity.[1] Immunogenicity has been described to affect various aspects of protein therapy, such as pharmacokinetics, pharmacodynamics and safety [67–70]. The ADAs are a result of an immune response, accomplished by B and T lymphocytes and antigen-presenting cells [67]; the same system contributing to the beneficial immune effects observed after vaccinations. In mAb therapy, in contrast to vaccination, it is desirable to keep the antibody production low. Factors known to contribute to an effective vaccination are, thus, best avoided [67, 68]. These and other factors described to influence immunogenicity, include (i) drug and drug-formulation attributes (e.g. adjuvants, aggregates, genetic origin of mAb); (ii) dosing regimen (repeated dosing, administration route); (iii) concomitant medication (e.g. reduced risk with immunosuppressants); and (iv) patient-specific characteristics (e.g. genetic deficiency, disease state, human leukocyte antigen type) [67, 68, 71]. Naturally, not all of these factors can be avoided or taken into consideration. Repeated dosing, for example, is required for treatment of some chronic diseases. There might, however, be ways of optimising the therapy to minimise the risk. It has been suggested that the risk is lower when infliximab is given as maintenance therapy than when given as episodic therapy [72]. Whether the immunogenicity is truly caused by the intermittent regimen or if it is a result of other underlying factors remains to be elucidated.

At present, the impact of ADAs on pharmacokinetics and pharmacodynamics is intricate to predict, both in adults and children. Firstly, there are challenges to overcome regarding the bioanalytical assays. Many (of the older) assays are not able to reliably quantify ADAs if the therapeutic mAb is present in the sample and/or are only able to detect a specific immunoglobulin subclass [73]. Secondly, ADAs are predominately polyclonal. This implies variations between and within individuals when it comes to the type of developed antibody (immunoglobulin class, neutralising/non-neutralising), their affinity to the mAb, their abundance and the persistency of the immunisation [70, 71]. Hence, there is not only one type of ADA—not even within one patient over time. Consequently, caution should also be taken when comparing ADA data from different bioanalytical assays as they might represent different species (e.g. different semi-quantitative measures).

The important issue of immunogenicity is currently gaining attention in the field, both when it comes to the issues of the bioanalytical assays [73, 74] and to new

[1] Many other abbreviations are also used in the literature, e.g. HAMA (human anti-murine antibodies), HACA (human anti-chimeric antibodies), HAHA (human anti-human(ised) antibodies); for some mAbs, specific abbreviations have been introduced, e.g. ATI (antibodies towards infliximab).

approaches on how to model the ADA impact on pharmacokinetics and pharmacodynamics [75]. These efforts will hopefully fill some of the gaps in this area in the coming years.

6.2 Developmental Aspects

Newborns have limited ability to produce an immune response compared with older children and adults, both in quantitative (lower production of, for example, cytokines or reduced number of IgG-producing B cells) and qualitative terms (e.g. reduced ability of cytokines to induce chemotaxis, reduced function of dendritic cells) [55, 76]. During early life the immune system is fine-tuning a variety of key functions as a result of stimulation from encountered environmental signals. The response patterns learnt in this period persists into adult life; a neonate has mostly naïve T lymphocytes, whereas in adults half of the T cell population are of memory phenotype [55]. It is reasonable to believe that these differences can cause differences in the occurrence and/or impact of the ADAs on pharmacokinetics and pharmacodynamics. At present, however, the literature provides more questions than answers: will it take longer for the ADAs to develop in children than in adults? What happens during early school years when the immune system is highly active? Moreover, the challenges described in the previous section also apply for data in children. More information is urgently needed in this field.

6.3 Anti-Drug Antibody Occurrence and Impact on Pharmacokinetics and Pharmacodynamics

Twenty-eight of the 54 studies evaluating pharmacokinetics of mAbs in children also reported the occurrence of ADAs (Tables 3 and 5), eight of which reported no detectable ADAs during the study period [63, 77–86]. These studies were in general short, with a low number of doses (single dose in four out of eight). The rest reported a proportion of ADA-positive (ADA^+) patients ranging from 2 to 77 %. In adults, the overall range of ADA occurrence is also large but the occurrence of each individual mAb is consistent with reports in children [3, 73, 75]. As previously mentioned, concomitant immunosuppressive medication has been described to affect ADA occurrence. Indeed, for adalimumab, a smaller proportion of ADA^+ patients was reported for the group with concomitant methotrexate [87, 88], as for in adults [13].

Despite the fact that ADA occurrence was reported in more than half of the 54 studies in this review, few reported any comment on its impact on the pharmacokinetics, especially in the paediatric (sub)population. For infliximab, ADA occurrence was included as a predictor of increased CL when using adult and paediatric data [50]. The paediatric data alone was not sufficient to identify this effect. Similarly, Robbie et al. [42] used adult and paediatric data and identified a high ADA titre as an important descriptor of CL, while low titres were concluded not to be clinically relevant. These examples support that mAb CL may be increased by immunogenicity, although the ADA quantitative relationship and impact on pharmacokinetics and pharmacodynamics need to be further explored, both in children and adults

7 Conclusions and Perspectives

Throughout this review, an exhaustive summary of pharmacokinetic and pharmacokinetic–pharmacodynamic characteristics of mAbs in children has been provided. Although a non-negligible number of studies evaluating pharmacokinetic characteristics was found, only a few examples comprehensively evaluated the pharmacokinetics/pharmacodynamics in children. Possible explanations for this situation could be an inadequate study design for pharmacokinetic analysis (e.g. sparse data) or inadequate analysis of the available data (EDCA vs. Pop. CMT). Limitations concerning the reporting of results have also been identified, complicating comparisons across studies and populations. Firstly, parameter information was reported in a very inconsistent fashion. The use of allometric scaling and normalising to a BW of 70 kg would enable easier comparison across studies as well as age groups [31]. Secondly, publication of model parameters and information regarding model-building strategies was incomplete. Publication of pharmacokinetic/pharmacodynamic models in full manuscripts rather than short abstracts, especially of internal models during drug development, could facilitate a better understanding and use of mAbs in children. All in all, these limitations constrained the ability to properly characterise pharmacokinetics with respect to body size and maturation and/or to establish relevant pharmacokinetic–pharmacodynamic relationships. Although not substantially covered in this review, drug–drug interactions also represent a poorly explored field that would benefit from further research.

The new EMA and FDA initiatives, requiring clinical drug research across age groups, will hopefully result in an increase in publically available information for this population. For future works, a ‘Guideline for Best Practice’ has been generated summarising aspects that should be considered when reporting pharmacokinetic and pharmacokinetic/pharmacodynamic studies in children (Box 1). This guideline will hopefully enable better comparisons, e.g. across studies, across the mAb drug class and with adult characteristics.

Box 1 'Guideline for Best Practice': reporting pharmacokinetic and/or pharmacokinetic–pharmacodynamic study results of monoclonal antibodies in children. *AUC* area under the plasma concentration–time curve, *CI* confidence interval, *CL* clearance, C_{min}. minimum concentration, *EBE* empirical Bayes estimate, *EDCA* exploratory drug concentration analysis, *Ind. CMT* individual compartmental analysis, *NCA* non-compartmental analysis, *Pop. CMT* population compartmental analysis, *RSE* relative standard error, t_{max}. time to maximum concentration

General recommendations

- ✓ Report the number of individuals
- ✓ Report the number of pharmacokinetic/pharmacodynamic samples and their respective sampling times
- ✓ Give full report of dosing regimens (dose, time, *and* duration of infusion)
- ✓ Give full report of all parameters (e.g. both volumes of distribution if reporting two-compartment model)
- ✓ Give full summary of relevant demographics for total population and evaluated subgroups, especially body weight and age
- ✓ Always consider and report anti-drug antibody development after multiple doses
- ✓ Always report pharmacokinetic and pharmacodynamic parameter units

EDCA / NCA

- ✓ C_{min} should always be accompanied with time after last dose
- ✓ *AUC* should always be accompanied with the time span it was calculated
- ✓ Report all possible parameters (e.g. also CL and not only *AUC* after intravenous administration
- ✓ t_{max} only relevant after extravascular administration

Ind. CMT / Pop. CMT

- ✓ Scale the population estimates allometrically to a body weight of 70 kg
- ✓ Report population estimates along with their imprecision (95% CI or RSE) - *not* descriptive statistics of EBEs
- ✓ Provide shrinkage, especially if EBEs are reported and covariate analysis was performed
- ✓ Report model development strategies

Population pharmacokinetic/pharmacodynamic modelling has proven to be an extremely valuable tool, especially in sparse data situations. It allows for (i) estimation of exposure-response relationships; (ii) quantification and explanation of variability; as well as (iii) prediction of the impact of variability and/or covariates on the final outcome. Once established, pharmacokinetic/pharmacodynamic models can thus enable a better understanding of differences between adult and paediatric patients and allow for a more rational drug use in the paediatric population, as, for example, has been shown for omalizumab. Similarly, physiologically based pharmacokinetic/pharmacodynamic models have been successfully used to adapt doses of small molecules to special populations (e.g. children). To develop these models, detailed knowledge on the impact of body composition, organ function and maturation processes on the pharmacokinetics/pharmacodynamics of mAbs is needed. In vitro data could be helpful to assess some of these aspects. Both modelling approaches could be used to optimise study designs (number of samples and individuals, and/or sample times), which is an important aspect in paediatric clinical trials.

In conclusion, limited information regarding the pharmacokinetics and, even more pronounced, pharmacokinetic–pharmacodynamic relationships of mAbs in children is available in the public domain. Further pharmacokinetic/pharmacodynamic studies are needed to allow for a more rational use of mAbs in the paediatric population, and also regarding the off-label use of mAbs in daily clinical practice. Furthermore, studies characterising maturation processes and biological differences between adults and children are needed to assess their potential impact on drug exposure and response. Wisely used, population approaches—combined with physiologically based pharmacokinetic/pharmacodynamic models or systems pharmacology approaches—can provide a global comprehension of the system.

Acknowledgments The authors wish to thank Corina Becker (Bayer Pharma) for fruitful discussion, Tamara Richter and Caroline Fongern (both Freie Universitaet Berlin) for their support during the literature search, and the reviewers of this manuscript for their valuable input into the manuscript. No sources of funding were used for the preparation of this review. The authors have no conflict of interest to declare.

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