Original Article

The Efficacy and Evidence-Based Use of Biologics in Children and Adolescents

Using Monoclonal Antibodies and Fusion Proteins as Treatments

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Summary

Background: Monoclonal antibodies (mAb) and fusion proteins (FP) are increasingly being used in children and adolescents. In this review, we analyze the evidence for their safety and efficacy in the treatment of the most common chronic inflammatory diseases.

Methods: We systematically searched PubMed, AWMF.org, and other databases for high-quality trials (i.e., randomized controlled trials with clinical primary endpoints) and guidelines published at any time up to 10 December 2018 that dealt with mAb and FP that are approved for pediatric use. The search term was “monoclonal antibody/fusion protein [e. g. adalimumab] AND children.”

Results: The 620 hits included 25 high-quality trials (20 of them manufacturer-sponsored) on 9 mAb/FP (omalizumab, adalimumab, etanercept, ustekinumab, infliximab, golimumab, anakinra, canakinumab, tocilizumab, and abatacept), as well as 6 guidelines (3 each of levels S3 and S2k) on the treatment of bronchial asthma, psoriasis, juvenile idiopathic arthritis, and chronic inflammatory bowel diseases. For none of these conditions are mAb and FP the drugs of first choice. Adverse drug effects are rare but sometimes severe (infection, immune dysregulation, tumors).

Conclusion: The retrieved trials have deficiencies that make it difficult to reliably evaluate the efficacy, safety, and utility of mAb/FP for children and adolescents with chronic inflammatory diseases. mAb/FP nonetheless represent a treatment option to be considered in case conventional immune-modulating drugs are ineffective. Researcher-initiated, high-quality trials and manufacturer-independent, systematic long-term evaluations of adverse effects (e.g., tumors) are sorely needed.

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Bronchial asthma (prevalence about 4%), psoriasis (about 0.7%), chronic inflammatory bowel disease (0.1%), and juvenile idiopathic arthritis (about 0.1%) are among the most common chronic inflammatory diseases in children. They are immune-modulated diseases (1–3). An important part in their pathogenesis is played by cytokines, including interleukin (IL)-1, IL-6 in juvenile idiopathic arthritis with systemic onset [sJIA], and tumor necrosis factor- α (TNF α) in polyarticular forms of juvenile idiopathic arthritis, psoriasis, and chronic inflammatory bowel disease) (*Figure 1*). Selective blockade of these cytokines by therapeutic monoclonal antibodies (mAb) and fusion proteins (FP) has the potential to intervene in the disease more specifically and less toxically than treatment with conventional immunomodulatory drugs (e.g., nucleoside analogs) that act nonspecifically on the metabolism of all cells. Nevertheless, adverse effects are also to be expected from monoclonal antibodies and fusion proteins, because the target antigens play an important part in the physiological immune response (e.g., TNF α in immunity to tuberculosis), and also because it must be assumed that “off-target” activity will occur, i.e., mAb/FP will bind nonspecifically to other antigens than the target (4–6).

mAb/FP are biologic agents and are substances that are produced by living organisms in a biological process, as distinct from a chemical process (*Figure 2*). They are administered parenterally and have a long half-life of up to 3 to 4 weeks (7–9). There is an insufficiency of data on the pharmacology of mAb/FP in children (among other things, dosage is given in “weight bands”, i.e. not strictly linearly according to body weight, and there is a lack of clarity about the extent to which data on adult dosages can be extrapolated to children, and about dosage increase during disease exacerbations).

The aim of the present article is to briefly present the standard (guideline-concordant) therapy of the most common chronic inflammatory diseases of children and adolescents, and then to analyze the available evidence for the efficacy and safety of mAb and FP in these diseases.

Methods

On 10 December 2018 a literature search was carried out on PubMed, awmf.org, and other databases for

published reports and guidelines on the use of approved mAb and FP in children and adolescents (*eMethods*, *eTable 1*). For the commonest chronic inflammatory diseases (with a prevalence $\geq 0.1\%$), we identified a total of 25 high-quality studies (i.e., that randomized mAb/FP against placebo or another intervention, and had clinical primary endpoints) that had investigated the efficacy of mAb/FP and had been included in guidelines.

Results

Bronchial asthma

Guideline-concordant therapy

In a stepped approach, short-acting inhaled β_2 -agonists as needed (step 1), leukotriene receptor antagonists (LTRA) or low/medium-dose inhaled corticosteroids (ICS) (steps 2 and 3), and long-acting β_2 -agonists, long-acting anticholinergics, or LTRA combined with medium- or high-dose ICS (steps 4 and 5) are used (10).

The indication for use of the mAb omalizumab, which targets immunoglobulin E (IgE), is based on high-quality studies and is given only in the last therapeutic step, step 6. The criteria are IgE-mediated asthma, positive skin test/in-vitro activity against a perennial airborne allergen, serum IgE concentration within the treatable range, and the elimination of avoidable allergen exposure.

State of the evidence

In four studies (two of them manufacturer-independent) of severe, refractory bronchial asthma, preseason administration of omalizumab was effective in terms of reducing the number of exacerbations during the fall and spring (11–14) (*eTable 2*).

Safety of omalizumab

In regard to children and adolescents, apart from the above-mentioned studies, little can be said because omalizumab is rarely used. The most frequent adverse effects are headache and reactions at the injection site (*Table*). Life-threatening anaphylactic reactions can occur hours or days after the injection, even when the antibody has been tolerated for a year or more (15).

Psoriasis

Guideline-concordant therapy

In patients with mild psoriasis, topical corticoids can be given first, alone or in combination with topical vitamin D derivatives (calcipotriol, tacalcitol) (16). In cases of moderate or severe psoriasis, systemic methotrexate p.o. or s.c. or adalimumab (for TNF α blockade) is indicated. If there is insufficient response to treatment, ustekinumab (IL-12 and IL-23 blockade) or etanercept (TNF α blockade) is recommended. The stated indication for adalimumab, etanercept, and ustekinumab is based partly on distorted data from high-quality studies. Regarding the use of other mAb/FP as a last resort, data from high-quality studies are lacking for the child and adolescent age groups. In

adults, the following have proved effective: infliximab, certolizumab pegol (TNF α blockade), guselkumab (IL-12, IL-23), ixekizumab, secukinumab (IL-17A), and brodalumab (IL-17 receptor A) (17, 18).

Studies in severe, refractory chronic plaque psoriasis
In a company-sponsored head-to-head study (adalimumab versus methotrexate), the results are distorted by a too-low initial dose of methotrexate in the control group (0.1 mg/kg body weight (BW)/week; standard dosage of methotrexate in inflammatory disease: 0.3 to 0.6 mg/kg BW/week) (19, 20). Etanercept and ustekinumab were more effective than placebo in terms of the Psoriasis Area and Severity Index (PASI 75) (21, 22) (*eTable 2*).

Safety (ustekinumab)

Ustekinumab is very rarely used in children and adolescents, and that only recently, so little systematically recorded experience has been accumulated. An increased incidence of infections is noted (*Table*).

Juvenile idiopathic arthritis and associated uveitis

Guideline-concordant therapy of juvenile idiopathic arthritis

With the nonsystemic forms of juvenile idiopathic arthritis (these include persistent oligoarthritis, enthesitis-related arthritis [EAA], and seronegative polyarthritis), conventional guideline-concordant treatment starts with nonsteroidal anti-inflammatory drugs (NSAIDs) and intra-articular injections of crystalloid glucocorticoids (e.g., triamcinolone hexacetonide) (23). At the next step up, methotrexate is given for a period of 6 months. If this is insufficiently effective, etanercept or adalimumab is indicated on the basis of studies with methodological weaknesses, in some cases quite considerable weaknesses (*Figure 3*). In the subtype of juvenile idiopathic arthritis with systemic onset (sJIA), steroid pulses are indicated, and if the steroids result in adverse effects or insufficient response, the IL-1 and IL-6 blocking drugs anakinra, canakinumab, or tocilizumab are indicated. The basis for their use is high-quality studies with in some cases very short observation periods (*eTable 2*).

State of the evidence

No high-quality studies are available for the most common form of juvenile idiopathic arthritis, persistent oligoarticular juvenile idiopathic arthritis. For the polyarticular form, in one independent and one company-sponsored study of TNF α blockers (etanercept, infliximab) the primary clinical endpoints were not reached (24, 25) (*eTable 2*).

In two open head-to-head studies, the combination of either etanercept or infliximab with methotrexate proved to be superior to monotherapy with methotrexate (juvenile idiopathic arthritis [ACR 70 and 75 respectively]), although in each case with a bias in favor of the combination containing TNF α blocker (26, 27). For the subtypes enthesitis-associated

Targeted blockade of the inflammatory reaction using monoclonal antibodies and fusion proteins

Naive T cells in the adaptive immune system are activated by means of antigens and costimulation (e.g., CD28 and CD80/CD86) and, through the mediation of cytokines, differentiated into antigen-specific T-helper cell subpopulations (TH1, TH2, and TH17 cells). In parallel to this, in the innate immune system macrophages are activated (e.g., directly via surface structures on bacteria, bacterial endotoxins, or viral nucleic acids, or indirectly via T cells) and these secrete proinflammatory cytokines. This results in chronic activation of various T-cell systems and to tissue destruction through the invasion of activated inflammatory cells into bronchial mucosa (in asthma: mast cells, eosinophils) or into skin, synovia, or intestinal mucosa (in psoriasis, chronic inflammatory bowel disease, juvenile idiopathic arthritis: lymphocytes, neutrophils). Monoclonal antibodies (mAb) and fusion proteins (FP) used in common inflammatory diseases are shown in red italics.

HLA, human leukocyte antigen/peptide complex; IgE, immunoglobulin E, IL, interleukin; IL12R, IL12 receptor, IL23R, IL23 receptor; MADCAM, mucosal addressin cell adhesion molecule; TCR, T cell receptor; TNF, tumor necrosis factor; VCAM, vascular cellular adhesion molecule

arthritis and juvenile ankylosing spondylitis, small studies have shown a reduction in the number of actively arthritic joints with adalimumab (28, 29). For systemic juvenile idiopathic arthritis, the IL-1 blocker canakinumab or the IL-6 blocker tocilizumab are effective (30–32). All other studies (including abatacept) used the withdrawal study design, which is inadequate for accurate measurement of efficacy (Figure 3) (33–39).

Guideline-compliant therapy of juvenile idiopathic arthritis-associated uveitis

As the first step, treatment is with topical steroids (40). If there is a threat of loss of vision, steroid

pulses are given until conventional immunomodulatory drugs (usually methotrexate) start to take effect. At the third step, although TNF α blockers (golimumab, adalimumab, infliximab) are recommended, high-quality evidence is available only for adalimumab (e1).

State of the evidence

In one independent study, adalimumab in combination with methotrexate was more effective in terms of an intraocular inflammation score than was methotrexate monotherapy (e1). By contrast, etanercept was shown in a very small study to be ineffective (e2).

FIGURE 2

The name of a monoclonal antibody is assembled from a sequence of syllables:

1. Prefix (to form a unique name)
2. Antepenultimate syllable (indicates the target or disease group)
3. Penultimate syllable (indicates the source of the antibody e.g., human, mouse, chimera, etc.)
4. Final syllable (indicates the nature of the protein: monoclonal antibody, receptor fusion protein)

Safety

TNF α blockers (etanercept, adalimumab, infliximab, golimumab) are usually well tolerated. The incidence of all severe adverse effects in the company-sponsored Pharma Child Register during the observation period for 8274 children with juvenile idiopathic arthritis was around 6% to 7% (e3). There is an increased risk (especially when combined with other immunomodulatory drugs) of the reactivation of tuberculosis and other infections, some of which may be severe (Table). The part played by mAb/FP in the development of cancer is the subject of debate, because juvenile idiopathic arthritis is itself associated with an increased risk of cancer (e4, e5). Diseases of immune dysregulation have been described, including demyelinating diseases, induction of uveitis (etanercept), and chronic inflammatory bowel disease (e6–e8).

IL-1 and IL-6 blockers are less frequently used than TNF blockers, and the cytotoxic T-lymphocyte associated protein 4 (CTLA-4) blockade even less often. Severe infections and immune dysregulation have been reported (Table), including six fatalities in the tocilizumab study and four in the canakinumab study in patients with systemic juvenile idiopathic arthritis; it is unclear whether there was a direct relation to the study medication (31, 32).

Chronic inflammatory bowel disease

Guideline-concordant therapy

When disease activity is mild in a child with Crohn's disease, enteral nutritional therapy (ENT) should be started, and if this fails and there is ileocecal involvement, budesonide should be given (e9). Where disease activity is moderate or severe, ENT should be used; systemic steroids and an immunomodulator

(azathioprine [AZA], 6-mercaptopurine [6-MP], methotrexate, and others) may also be given. Despite a lack of high-quality studies, TNF α blockers (adalimumab, infliximab) are recommended for treatment and maintenance of remission if conventional immunomodulators (steroids, AZA, 6-MP, methotrexate) fail.

In patients with ulcerous colitis, to induce remission of mild or moderately active proctitis, first mesalazine is given as a suppository only; unlike in Crohn's disease, ENT has little effect (e10).

If this fails, topical steroids are added. To induce remission of mild to moderate ulcerous colitis, combined treatment with rectal and oral mesalazine is given. If this fails, the next step is to use systemic steroids and immunomodulators (AZA, 6-MP) or TNF α blockers (infliximab, adalimumab). Severe exacerbations are treated initially with a systemic steroid and/or with TNF α blockers, CSA/tacrolimus, or thiopurines; in some cases proctocolectomy may be necessary. To intensify maintenance of remission, depending on preceding treatment, 5-ASA, thiopurine, a TNF α blocker, or the integrin inhibitor vedolizumab is used. As in Crohn's disease, there is no scientific evidence that mAb are effective in children and adolescents.

State of the evidence

In one meta-analysis in adults with moderate to severe Crohn's disease, infliximab or adalimumab were effective in inducing remission; in ulcerous colitis only infliximab was effective (e11). The relatively widespread use of mAbs in chronic inflammatory bowel disease in children is based exclusively on the above-mentioned adult data and numerous lower-quality studies of mAb, all of which lacked the appropriate control groups to prove efficacy. In regard to vedolizumab, no controlled studies have been carried out in children (e12).

Safety

TNF α blockers have been used for many years in chronic inflammatory bowel disease, and on the whole are well tolerated. Very rarely, patients with chronic inflammatory bowel disease develop hepatosplenic T-cell lymphoma, which has a high mortality rate. The lymphoma has been linked to the combination of AZA and infliximab, but was seen even before the era of biologic agents (e13). Vedolizumab has only recently come into use, is very rarely used in children and adolescents, and no systematic data collection has been carried out.

Discussion

Care aspects of the use of mAb/FP

In all the treatment guidelines for the diseases discussed in this article, it is seen as important for children and adolescents to be under the care of, not just their local pediatrician, but also pediatric specialists (e.g., pediatric pneumologist, pediatric rheumatologist, pediatric hematologist, pediatric nephrologist, pediatric

TABLE

FDA- and EMA-approved monoclonal antibodies*¹ and fusion proteins (mAb/FP), listed by target antigens, for which high-quality efficacy studies (for definition, see eMethods) are available for the most common chronic inflammatory diseases in children and adolescents

Target system	Target	mAb/FP, name ^{*2}	Type of mAb/FP	Admin.	FDA/EMA	Adverse effects ^{*3} (e23–e29)
Lymphocytes						
T cell/APC	CD80, CD86	Abatacept Orencia	FP, CTLA4-IgG	iv /sc	RA, JIA	Immune dysregulation: Steven–Johnson syndrome, TEN, colitis, endocrinopathies, OI as a sequela of treatment for immune dysregulation
Cytokines						
TNF	TNFα	Adalimumab , Humira, Hefiya, Amgevita, Imraldi, Hyrimoz, Hulio, Idacio, Kromea	mAb, human	sc	RA, JIA, PA (FDA only), CD, PP, uveitis (EMA only)	Infections: Reactivation of TB and hepatitis B and C, SBI (sometimes with intracellular pathogens) and viral infections, OI (histoplasmosis, PJP, candidiasis, aspergillosis)
	TNFα, TNFβ	Etanercept Enbrel, Lirfior, Benepali, Erelzi	FP, TNFR-IgG1 Fc	iv	RA, JIA, PA, MC (FDA only), PP	Immune dysregulation: Fatal infusion reactions, cytopenia, CIDP, psoriasis, cutaneous lupus, necrotizing vasculitis, dermatomyositis, polymyositis, antiphospholipid antibody syndrome, CIBD
	TNFα	Infliximab Remicade, Remsima, Inflectra, Zessly	mAb, chimeric (mouse)	iv	RA, AS, PA, PP, MC, UC	Etanercept: Induction of uveitis Tumors: Lymphoma, melanoma, other skin cancer
	TNFα	Golimumab Simponi	mAb, human	sc	RA, AS, PA (FDA only), JIA (EMA only)	Other: Cardiomyopathy, cardiac dysrhythmias, bowel obstruction, ADEM, peripheral neuropathy, Guillain–Barré syndrome, multifocal motor neuropathy
IL-1	IL-1R Typ I	Anakinra Kineret	human IL-1Ra	sc	RA, sJIA (EMA only), CAPS (EMA only)	Infections: SBI, bacterial and viral infections, fatal myocarditis
	IL-1β	Canakinumab Ilaris	mAb, human	sc	CAPS, TRAPS, FMF, HIDS/MKD (EMA only), sJIA, gout (EMA only)	Immune dysregulation: Pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, dermatitis, encephalitis, psoriasis, vitiligo, neutropenia
IL-6	IL-6R	Tocilizumab Actemra, RoActemra	mAb, humanized	iv	RA, JIA	Infections: SBI, OI (aspergillosis, candidiasis, PJP) Immune dysregulation: Anaphylactic reaction, fatal MAS, psoriasis, vasculitis Other: Pneumothorax, fatal pulmonary hypertension, heart failure, gastrointestinal bleeding, diverticulitis, gastrointestinal perforation, PRES
IL-12/IL-23	p40 Chain IL-12, IL-23	Ustekinumab Stelara	mAb, human	sc	Psoriasis (FDA only)	Infections: Nasopharyngitis, candidiasis (mucosae), sinusitis, viral infections, diverticulitis, cellulitis, pneumonia, appendicitis, sepsis, osteomyelitis, cholecystitis, gastroenteritis, bronchitis, urinary tract infections Immune dysregulation: Leukoencephalopathy, induction of psoriasis (paradoxical reaction) Tumors: Skin melanoma Other: Headache, fatigue, dizziness, joint pain
Antibody						
IgE		Omalizumab Xolair	mAb, humanized	iv	Severe asthma ≥ 12 years (FDA), ≥ 6 years (EMA)	Infections: Upper airways, viral gastroenteritis, worm infestation Immune dysregulation: Anaphylactic reaction, fever, eosinophilia, serum sickness Other: Headache, stomach ache, nose bleed, skin reaction at injection site

*¹ List of FDA-approved antibodies at https://en.wikipedia.org/wiki/Monoclonal_antibody_therapy

*² Generic name, brand name (including names of biosimilars)

*³ FDA prescribing information; many of the adverse effects were described during comedication with other immunomodulators.

ADEM, acute disseminated encephalomyelitis; Admin., administration; APC, antigen-presenting cell; AS, ankylosing spondylitis; CAPS, cryopyrin-associated periodic syndrome; CD, Crohn's disease; CIBD, chronic inflammatory bowel disease; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; FMF, familial Mediterranean fever; FP, fusion proteins; HIDS/MKD, hyper-IgD syndrome/mevalonate kinase deficiency; IL-1, interleukin-1; IL-1Ra, interleukin-1 receptor antagonist; IL-1RI, interleukin-1 type I receptor; IL-1R, IL-1 receptor; IL-1R-AP, IL-1 receptor accessory protein; IL-2R, interleukin-2 receptor; IL-6, interleukin-6; IL-6R, interleukin-6 Receptor; JIA, juvenile idiopathic arthritis; mAb, monoclonal antibody; MAS, macrophage activation syndrome; OI, opportunistic infections; PA, psoriatic arthritis; PJP, *Pneumocystis jirovecii* pneumonia; PP, plaque psoriasis; PRES, posterior reversible encephalopathy syndrome; SBI, severe bacterial infections; TB, tuberculosis; TEN, toxic epidermal necrolysis; RA, rheumatoid arthritis; sJIA, juvenile idiopathic arthritis with systemic onset; TNF, tumor necrosis factor; TRAPS, TNF-receptor-associated periodic syndrome; UC, ulcerative colitis

FIGURE 3

Poor-quality study design (“withdrawal design”). This study design measures not the efficacy of the study drug after the start of treatment, but its apparent efficacy after treatment has stopped (measured by the occurrence of disease exacerbations). In phase 1, all patients are given the study drug (“open-label lead-in”). This design results in an apparently high response rate, since it has been shown that 35% (20% to 47%) of all probands with juvenile idiopathic arthritis experience a placebo effect (e20) when given a new drug. Before phase 2, all patients who have not responded are excluded from the trial; for this reason, this study design is also referred to as “enriched design” (e21). All patients experiencing a placebo effect are automatically included within this design, because they respond to the treatment. The result is marked distortion of the true effect of the study drug (biologic). Since all patients receive the study drug in phase 1, and monoclonal antibodies have a long half-life, significant differences in adverse effects between groups A and B during phase 2 cannot be identified, and so the design produces data showing an apparently low incidence of adverse effects (e22).

gastroenterologist) in centers where decisions regarding treatment with mAb/FP are usually made. For a successful treatment outcome, an interdisciplinary approach is always important, drawing on expertise in dermatology, ophthalmology, surgery, physiotherapy, and others.

Value of mAb/FP in comparison to standard immunomodulators

For none of the diseases analyzed here are mAb or FP the treatment of first choice. In the treatment of asthma, omalizumab is safe, but appears only in the very last treatment step and is rarely contemplated. In psoriasis, in polyarticular and nonsystemic forms of juvenile idiopathic arthritis, enthesitis-related arthritis, juvenile idiopathic arthritis-associated uveitis, and chronic inflammatory bowel disease, mAb/FP are only used when steroids/conventional immunomodulators (e.g., methotrexate in juvenile idiopathic arthritis, 5-acetylsalicylic acid, thiopurine in chronic inflammatory bowel disease) are insufficiently effective or are not tolerated. In children, oral administration of conventional immunomodulators can be associated with compliance problems (e.g., aversion to methotrexate). Whether parenteral administration of mAb/FP is better remains, in the absence of comparative studies, an open question.

In systemic juvenile idiopathic arthritis, while it is true that IL-1 and IL-6 blockers carry safety risks such as severe infection, they are effective and may be of greater benefit than steroid pulses. No high-quality studies on this topic exist.

Safety assessment of mAb/FP compared to standard immunomodulators

Since severe infusion reactions can occur with mAbs, the first administration is usually monitored in the inpatient or daypatient setting. Because of the inadequacy of existing evidence (lack of high-quality comparative studies against conventional immunomodulators, inhomogeneous definitions of severe adverse effects, low patient numbers, very short observation periods), it remains unclear whether the safety of mAb/FP is comparable to that of conventional immunomodulators. Severe adverse effects and deaths are not always adequately detailed in company-sponsored studies, or are not mentioned in core elements of publications (e.g., abstracts) (31, 32).

Quality of mAb/FP studies and scope for improvement

Many uncontrolled studies have been carried out on mAb/FP. In its recommendations on the ethics of carrying out clinical studies in children, the European Medicines Agency (EMA) rejects uncontrolled studies as a basis for evidence of efficacy, and recommends study designs that minimize bias (e14).

Many company-sponsored registers are collecting long-term data on mAb/FP. These are often used as a basis to determine the efficacy and safety of these substances in children with chronic inflammatory diseases. The use of registry data to investigate cause-and-effect relationships is inappropriate (e15). There is a risk that ‘facts’ will be created from registry data that lack deep scientific underpinnings. One example of current healthcare provision for children and

adolescents with rheumatic disease is the prescription in 2017 of mAb/FP to >10% (319/3006) of children with the most common form of juvenile idiopathic arthritis (so-called persistent oligoarticular juvenile idiopathic arthritis) in the absence of evidence from a single high-quality study (e16).

Our analysis shows that only 20% of studies (5/25) classified as high-quality were carried out independently of pharmaceutical companies. To improve the evidence regarding the use of mAb/FP, more researcher-initiated studies with the following characteristics are needed:

- Classical double-blind, randomized study design; in particular, more head-to-head trials of TNF α blockers versus methotrexate/thiopurine (juvenile idiopathic arthritis/chronic inflammatory bowel disease) or IL-1/IL-6 blockers versus cortisone pulses (systemic juvenile idiopathic arthritis)
- Longitudinal studies (e.g., 6 to 12 months) with a large enough number of patients, in order to capture chronic diseases with a relapsing course over months or years better than is possible with a short observation period of 12 or at most 16 weeks
- Cohort studies and pharmacovigilance registries (like the German Child Cancer Registry, *Deutsches Kinderkrebsregister*) that are independent of pharmaceutical companies
- Studies on the pharmacokinetics of mAb/FP.

Conclusion

The UN Convention on the Rights of the Child guarantees a child's right to the highest attainable standard of health (article 24, paragraph 1), and this includes the highest standard of evidence for interventions (e17). The mAb/FP studies suffer from qualitative weaknesses that make it difficult to assess the efficacy and safety of mAb/FP. Despite the unsatisfactory state of the evidence, and the adverse effects, some of which can be severe, mAb and FP do represent a therapeutic option for children and adolescents in whom conventional immunomodulatory treatment is insufficiently effective. When there is a risk of severe complications of a chronic inflammatory disease in a child or adolescent, the use of mAbs and FPs, after a calculation of the risks and benefits, can be justified.

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Professor Niehues has received authorship fees from uptodate.com (Wellesley, Massachusetts, USA) and reimbursement of travel expenses during consultancy work for the European Medicines Agency (EMA), steering committees of the PENTA Paediatric European Network for Treatment of AIDS (Padua, Italy), the Juvenile Inflammatory Cohort (JIR) (Lausanne, Switzerland), and, until 2017, the FIND-ID Initiative (supported by the Plasma Protein Therapeutics Association [PPTA] [Brussels, Belgium]). Dr. Turul Özgür declares that no conflict of interest exists.

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Key messages

- The pathogenesis of the most common chronic inflammatory diseases in children and adolescents (asthma, chronic inflammatory bowel disease, psoriasis, and juvenile idiopathic arthritis) is multifactorial, and is as yet insufficiently understood for us to be able to intervene in the pathological mechanism with adequate precision using monoclonal antibodies and fusion proteins (mAb/FP).
- mAb/FP can have significant adverse effects, which can in some cases be life-threatening.
- A large proportion of studies on mAb/FP have severe qualitative weaknesses, making it very difficult to assess the efficacy and safety of these drugs.
- The use of mAb and FP is a therapeutic option in children and adolescents where conventional immunomodulators fail to be effective and there is a risk of disease complications.
- Good communication between the primary care pediatrician and pediatric specialists is an important requirement, enabling early action in case of treatment failure or adverse effects (e.g., fever or unexplained weight loss as warning signs of treatment-related infection or malignancy).

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► **Supplementary material**

For e-References please refer to:
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Supplementary material to:

The Efficacy and Evidence-Based Use of Biologics in Children and Adolescents

Using Monoclonal Antibodies and Fusion Proteins as Treatments

by Tim Niehues and Tuba Turul Özgür

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eMETHODS

The systematic literature search was carried out using the search term “monoclonal antibody/fusion protein and children” (e.g., “adalimumab and children”) with filters “clinical trial,” “human” (species), “English” (language), “0–18 years” (age), and “abstract available,” and found 620 studies (*eTable 1*). Twenty-five high-quality studies of common chronic inflammatory diseases were identified.

Studies meeting the following descriptions were excluded: studies of rare inflammatory or monogenetic diseases (e.g., nephrotic syndrome, cryopyrin-associated periodic syndrome [CAPS], atypical hemolytic-uremic syndrome [aHUS]), or inflammatory diseases in which no evidence of efficacy of monoclonal antibodies and fusion proteins (mAb/FP) in children and adolescents was shown (e.g., diabetes mellitus), and/or studies of mAb/FP not mentioned in guidelines (e.g., omalizumab and seasonal allergic rhinitis); studies in the field of stem cell and organ transplantation research (a large field in its own right), infections (e.g., respiratory syncytial virus [RSV] infection), vascular disease (e.g., retinopathy of prematurity), or cancer (neuroblastoma); studies that mainly focused on and recruited adults; studies that focused on costs, or the diagnostic use of mAb or FP, or their perioperative use.

The following study designs were assessed as relatively poor in quality and were excluded: noninferiority studies imply efficacy of the study drug, which in the absence of evidence of efficacy in preliminary studies may not actually exist (e18). Studies lacking a placebo or drug control group, registry or cohort studies, phase I and II studies (safety, dosage), follow-up studies (“follow-up”, “open-label extension”), subgroup analyses, pilot studies, studies of study design, surveys, questionnaires, and studies in which the placebo phase is randomized (“randomized placebo-phase design,” which measures the time to response to a therapeutic intervention, but not the efficacy) (e19).

eTABLE 1

Results of the literature search*: high-quality studies of efficacy (in relation to clinical endpoints) of FDA-approved monoclonal antibodies and fusion proteins (versus placebo or versus established therapies) in children and adolescents with common chronic inflammatory diseases

mAb, fusion protein (FDA-approved)	(n =)	After exclusions (=)	First author, journal, year, (disease)
Abatacept	11	1	Ruperto, Lancet, 2008 (JIA)
Abciximab	3	0	–
Adalimumab	26	5	Papp, Lancet, 2017 (psoriasis) Ramanan, N Engl J Med, 2017 (uveitis) Burgos-Vargas, Arthr Care Res, 2015 (JIA subtype EAA) Horneff, Arthr Res Ther, 2012 (JoAS) Lovell, N Engl J Med, 2008 (JIA, JIA subtype EAA)
Aflibercept	1	0	–
Alemtuzumab	42	0	–
Anakinra	21	1	Quartier, Ann Rheum Dis, 2011 (sJIA)
Basiliximab	33	0	–
Benralizumab	2	0	–
Bevacizumab	29	0	–
Blinatumomab	3	0	–
Brentuximab vedotin	4	0	–
Burosumab	1	0	–
Canakinumab	19	1	Ruperto, N Engl J Med, 2012 (sJIA)
Cetuximab	1	0	–
Daclizumab	23	0	–
Denosumab	1	0	–
Dinutuximab	11	0	–
Dupilumab	3	0	–
Eculizumab	5	0	–
Emicizumab	3	0	–
Erenumab	2	–	–
Etanercept	55	6	Hissink Muller, Pediatr Rheumatol Online J, 2017 (JIA) Horneff, Arthr Rheum, 2015 (EAA-JIA) Wallace, Arthr Rheum, 2012 (JIA) Paller, N Engl J Med, 2008 (psoriasis) Smith, Arthr Rheum, 2005 (uveitis) Lovell, N Engl J Med, 2000 (JIA)
Gemtuzumab	24	0	–
Golimumab	2	1	Brunner, Ann Rheum Dis, 2018 (JIA)
Guselkumab	0	0	–
Ibritumomab tiuxetan	1	0	–
Ibalizumab	0	0	–
Infliximab	64	2	Tynjälä P, Ann Rheum Dis, 2011 (JIA) Ruperto, Arthr Rheum, 2007 (JIA)
Inotuzumab ozogamicin	3	0	–
Ipilimumab	2	0	–
Mepolizumab	6	0	–
Natalizumab	2	0	–
Ofatumumab	2	0	–
Omalizumab	75	4	Teach, J Allergy Clin Immunol, 2015 (asthma) Busse, N Engl J Med, 2011 (asthma) Lanier, J Allergy Clin Immunol, 2009 (asthma) Milgrom, Pediatrics, 2001 (asthma)

mAb, fusion protein (FDA-approved)	(n =)	After exclusions (=)	First author, journal, year, (disease)
Pavlizumab	30	0	–
Pertuzumab	1	0	–
Ranibizumab	3	0	–
Reslizumab	3	0	–
Rilonacept	5	0	–
Rituximab	80	0	–
Rituximab and hyaluronidase	0	0	–
Sarilumab	0	0	–
Tildrakizumab	4	0	–
Tocilizumab	12	3	Brunner, Ann Rheum Dis, 2015 (JIA) de Benedetti, N Engl J Med, 2012 (sJIA) Yokota, Lancet 2008 (sJIA)
Trastuzumab	0	0	–
Ustekinumab	2	1	Landells, J Am Acad Derm, 2015 (psoriasis)
Vedolizumab	0	0	–
N = 47 mAb/FP	620	25	

*¹ PubMed search strategy: monoclonal antibody (by name) and "children," e.g., "eculizumab AND children" (PubMed filters: "clinical trial," "human," "English," "0–18," "text availability: abstract"; FDA-approved monoclonal antibodies from Wikipedia list at https://en.wikipedia.org/wiki/Monoclonal_antibody_therapy as of 10 December 2018.

Exclusion criteria: see *eMethods*

EAA, enthesitis-related arthritis; FP, fusion protein(s); JIA, juvenile idiopathic arthritis; JoAS, juvenile-onset ankylosing spondylitis; mAb, monoclonal antibody/ies; sJIA, systemic JIA

eTABLE 2

High-quality studies (n = 25) (for definition, see eMethods) of the use of monoclonal antibodies and fusion proteins (mAb and FP) in the most common chronic inflammatory diseases with efficacy as the primary clinical endpoint, listed by disease

Target: mAb/FP First author, ref. (sponsor ¹)	Age (in years)	n	Duration ²	Primary clinical endpoint, outcome, significance level	Remarks
Refractory IgE-mediated allergic bronchial asthma					
IgE: omalizumab					
Teach (11)	6–17	478	4 months	Patients (%) with asthma exacerbation ³ . Verum: 11.3%, placebo: 21%; p <0.05	Study group with particular characteristics ("inner city populations", USA); no data on quality of life or mortality
Busse (12)	6–20	419	60 weeks	Number of days with symptoms in a 2-week period ⁴ . Verum: 1.48, placebo: 1.96; p ≤ 0.001	
Lanier (13) (Novartis)	6–12	627	52 weeks	Incidence of asthma exacerbations in a 24-week period ⁵ . Verum: 0.45, placebo: 0.64; p = 0.007	
Milgrom (14) (Genentech)	6–12	334	28 weeks	Reduction (%) in inhaled corticosteroid dose. Verum: 100%, placebo: 66.7%; p = 0.001	
Severe refractory chronic plaque psoriasis					
TNFα: adalimumab; etanercept					
Adalimumab Papp (20) (AbbVie)	4–18	114	16 weeks	Patients (%) with PASI 75 ⁶ and PGA score clear skin (0) or almost clear skin (1) Verum: 58% (high dose), 44% (low dose), methotrexate 32%; p = 0.002; p = 0.027	Adalimumab more effective than methotrexate (but methotrexate dosage was too low), etanercept effective
Etanercept, Paller (21) (Immunex, Wyeth)	4–17	211	12 weeks	Patients (%) with PASI 75, verum: 57%, placebo: 11%; p <0.001	
IL-12 and IL-23: ustekinumab					
Landells (22) (Janssen)	12–17	110	12 weeks	Patients (%) with PGA 0/1 Verum: (high and standard dose) 67.6%; 69.4%, Placebo: 5.4%; p <0.001	Low patient numbers
Refractory ⁷ systemic juvenile idiopathic arthritis					
IL-6: tocilizumab					
de Benedetti (32) (Hoffman La-Roche)	2–17	112	12 weeks	Patients (%) with JIA ACR 30 ⁸ and no fever Verum: 85%, placebo: 24%; p < 0.001	Short study duration
Yokota (33) (Chugai)	2–19	43	12 weeks	Patients who maintained JIA ACR 30 ⁸ after withdrawal of tocilizumab, CRP concentration <15 mg/L Verum: 80%, placebo: 17%; p ≤ 0.0001	Poor-quality withdrawal design
IL-1: canakinumab, anakinra					
Canakinumab Ruperto (31) (Novartis)	2–19	84	4 weeks	Patients (%) with JIA ACR 30 ⁸ Verum 84%, placebo 10%; p <0.001	Very short study duration Low patient numbers
Anakinra Quarier (30) (Amgen)	2–20	24	4 weeks	JIA ACR 30 Regression of systemic symptoms 50% reduction in CRP, erythrocyte sedimentation rate verum: 8/12, placebo: 1/12; p = 0.003	Very short study duration Low patient numbers

Target: mAb/FP First author, ref. (sponsor ^{†1})	Age (in years)	n	Duration ^{*,2}	Primary clinical endpoint, outcome, significance level	Remarks
Refractory^{*,7} enthesitis-related arthritis; juvenile onset ankylosing spondylitis (JOAS)					
TNFα: adalimumab, etanercept					
Adalimumab (enthesitis-related arthritis) Burgos-Vargas (28) (AbbVie)	6–17	46	12 weeks	Change (%) in the number of joints with active arthritis Verum: –62.6%, placebo: –11.6%; p = 0.039	Short study duration Low patient numbers
Etanercept (enthesitis-related arthritis) Homeff (34) (Pfizer)	6–18	38	24 weeks	Patients with arthritis flare-up ⁹ Verum: 3/12, placebo: 9/12; p = 0.02	Poor-quality withdrawal design
Adalimumab (JOAS) Homeff (29) (Abbott)	12–17	32	12 weeks	Patients (%) with ASAS40 ^{*,10} Verum: 53%, placebo: 33%; p > 0.05	Endpoint not attained, very short study duration, low patient numbers
Refractory^{*,7} polyarticular juvenile idiopathic arthritis					
CD80/CD86: abatacept					
Ruperto (35) (Bristol-Myers)	6–17	122	10 months	Patients (%) with arthritis flare ^{*,9} Verum: 20%, placebo: 53%; p = 0.0003	Poor-quality withdrawal design
TNFα: adalimumab; etanercept, infliximab; golimumab					
Adalimumab Lovell (36), (Abbott)	4–17	75	32 weeks	Patients (%) with arthritis flare ^{*,9} Verum: 43%, placebo: 71%; p = 0.03	Poor-quality withdrawal design
Etanercept Wallace (25)	2–16	85	24 weeks	Clinically inactive disease ^{*,11} Verum: 40%, placebo: 23%; p = 0.088, not significant	Endpoints not reached despite additional steroids in the verum group
Etanercept Lovell (37) (ImmuneX)	4–17	51	16 weeks	Patients (%) with JIAACR 30 ^{*,8} Verum: 28%, placebo: 81%; p = 0.003	Poor-quality withdrawal design
Etanercept Hissink Müller (27) (Pfizer) (patients with oligoarthritis were included)	2–16	94	12 weeks	Patients (%) with JIAACR 30, 50, 70 ^{*,8} Etanercept + methotrexate 73%; 53%, 47% Methotrexate or sulfasalazine 50%, 31%, 25% Methotrexate and steroids 53%, 38%, 19% p = 0.04 only for JIAACR 70 Other comparisons not significant	Open, no placebo group Bias in favor of etanercept Minimal improvement seen only in combination with methotrexate
Infliximab Ruperto (24) (Centocor Inc.) (patients with oligoarthritis were included)	4–17	122	14 weeks	Patients (%) with JIAACR 30 ^{*,8} Verum: 63.8%, placebo: 49.2%; p = 0.12, not significant	Endpoints not reached
Infliximab Tynjälä (26)	4–15	60	54 weeks	Patients (%) with JIAACR 75 ^{*,8} Infliximab + methotrexate: 100%, Methotrexate: 50%; Methotrexate + sulfasalazine + hydroxychloroquine: 65%; p < 0.0001	Open, no placebo group Bias in favor of infliximab Inadequate randomization
Golimumab; Brunner (39) (Janssen)	2–17	154	32 weeks	Patients (%) with arthritis flare ^{*,9} Verum: 41%, placebo: 47%; p = 0.41, not significant	Poor-quality withdrawal design Endpoints not reached

Target: mAb/FP First author, ref. (sponsor ^{*1})	Age (in years)	n	Duration ^{*2}	Primary clinical endpoint, outcome, significance level	Remarks
IL-6: tocilizumab					
Brunner (38) (Hoffmann-La Roche)	2–17	163	24 weeks	Patients (%) with arthritis flare ^{*9} Verum: 25.6%, placebo: 48.1%; p = 0.0024	Poor-quality withdrawal design
Refractory^{*7} juvenile idiopathic arthritis-associated uveitis					
TNF: adalimumab; etanercept					
Ramanan (e1)	2–18	90	18 months	Patients (%) in whom treatment failed (as defined by score for intraocular inflammation) ^{*12} , Verum: 27%, placebo: 60%; p < 0.0001	Endpoint (cell count in the anterior chamber in children) not validated
Smith (e2) (Immunex)	6–15	12	6 months	Ophthalmologic success/failure ^{*13} , Verum: 3/7; 1/7; placebo: 2/5; 1/5; p = 1; p = 0.58	Very low patient numbers Endpoints not reached

^{*1} Where no information is given, study was independent

^{*2} Observation period during which the intervention (study medication) was tested against placebo or other intervention. (The timepoint at which the clinical endpoint was measured does not include open-label extension phases.)

^{*3} Worsening of asthma control requiring systemic corticosteroids or hospitalization within 90 days (from the first day of each participant's school year)

^{*4} Number of days with wheezing, chest tightness, or cough; number of nights with disturbed sleep; number of days on which normal activity was restricted

^{*5} Exacerbation of asthma symptoms requiring doubling of baseline dose of inhaled corticosteroids and/or treatment with systemic corticosteroids for ≥ 3 days

^{*6} Psoriasis Area and Severity Index, which combines the assessment of the severity of lesions and the area affected into a single score in the range 0 (no disease) to 72 (maximal disease). The body is divided into four sections for assessment of the extent of involvement (0 to 100%) and each section scored for erythema, induration, and desquamation (grades 1–4). PASI 75 gives the percentage of patients whose PASI score went down by 75% or more from baseline. PGA, Physician Global Assessment

^{*7} Refractory to first-line therapy (e.g., intra-articular and/or systemic steroids, steroid-based eye drops, nonsteroidal antiinflammatory drugs, methotrexate/disease-modifying antirheumatic drug (DMARD), or other biologic agents)

^{*8} JIA ACR 30 (or 50, 70, 75): Improvement by 30% (or 50%, 70%, 75%) or more in three or more of the six variables of the ACR core outcome variables for JIA: (1) PGA (10-cm visual analog scale), (2) functional ability, (3) number of joints with active arthritis, (4) number of joints with limited range of movement, and (5) ESR, with no more than one variable that has worsened by more than 30%.

^{*9} Definition of an arthritis flare: recurrence of fever for 2 or more consecutive days; ≥ 30% worsening of three or more of the six ACR core outcome variables for JIA with not more than one variable that has improved by more than 30%, or worsening of at least two joints with limited range of movement, with at least one worsening by 20 mm on the PGA visual analog scale as assessed by the physician or the parents

^{*10} ASAS40: Assessment of Spondyloarthritis International Society 40; criteria encompass four areas: patient global assessment, pain, function, and inflammation

^{*11} Clinically inactive disease: no joint with active arthritis; no fever, skin rash, serositis, splenomegaly, or generalized lymphadenopathy that can be ascribed to JIA; no active uveitis; ESR in the normal range; PGA score 0

^{*12} SUN criteria for intraocular inflammation(40)

Failure defined as: AC cells >1+ in the eye and topical corticosteroid ≥3× daily after 4 months of treatment; development of a sight-threatening inflammatory ophthalmic lesion requiring immediate increase in systemic anti-inflammatory therapy or a perocular injection of corticosteroids

ACR, American College of Rheumatology; ESR, erythrocyte sedimentation rate; IgE, immunoglobulin E; IL-1, interleukin 1; IL-6, interleukin 6; IL-1RI, interleukin-1 type 1 receptor; IL-2R, interleukin 2 receptor; PGA, Physician Global Assessment; pJIA, polyarticular juvenile idiopathic arthritis; TNF, tumor necrosis factor