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Biologic-Associated Infections in Pediatric Rheumatology

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Abstract During the past 15 years, biologics for juvenile idiopathic arthritis (JIA) therapy has led to new options. However, despite the high effectiveness and safety profile of these agents, infections are of great concern. The risk for bacterial infections, which appears to be increased in JIA patients as a result of the disease itself, seems to be increased further by antirheumatic treatment. Combining data from several sources, infection rates appear to be comparable for abatacept (1.33/100 person-years (PY); 95 % confidence interval (CI)=0.50–2.48), adalimumab (1.42/100 PY; 1.01–1.99), and etanercept (1.28/100 PY; 1.06–1.55); higher with golimumab (3.03/100 PY; 1.26–7.29) and infliximab (3.42/100 PY; 1.71–6.84); and even higher with tocilizumab (8.62/100 PY; 6.69–11.10). The rate of serious infection was lowest with methotrexate (0.67/100 PY; 0.48–0.93). In patient cohorts treated with methotrexate without a biologic as a comparator, risk ratios for serious infections were significantly increased for all biologics, except abatacept, because of insignificant patient numbers. Opportunistic infections, including tuberculosis, were very rare. Herpes zoster was the only specific infection occurring frequently throughout the studies. Thus, the safety profiles of approved biologics are highly acceptable. Although this conclusion is based on limited experience and is not easily expanded to the interleukin (IL)-1 inhibitor canakinumab or the T cell activation inhibitor abatacept, both these agents have demonstrated an excellent safety profile so far.

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Introduction

As recently as 15 years ago, a diagnosis of juvenile idiopathic arthritis (JIA) often meant a lifetime of pain and disability. However, with the introduction of biologics such as anti-tumor necrosis factor alpha (TNF-α) agents or antagonists to interleukin (IL)-1 or IL-6 or B or T cell inhibitors, inactive disease and remission of JIA are now within reach of most patients [1, 2]. TNF antagonists were the first of these agents to be used, and their effectiveness in JIA is well proven [3–9]. However, immunosuppressive and immunomodulatory treatment with corticosteroids and immunosuppressants such as methotrexate, cyclosporine A, azathioprine, and others, as well as the biologics, works by inhibiting the immune system, resulting in increased susceptibility to infections. Therefore, data regarding long-term safety, especially those regarding infections, are important.

Data used to evaluate the long-term safety of biologic therapies are derived from controlled trials performed for drug approval, extension studies of the original clinical trials, and national registries. Although extension studies usually have a prospective design, long-term follow-up cannot be placebo controlled for ethical reasons. Also, patient numbers tend to be relatively small and tend to decrease over time. Therefore, these studies often are underpowered for analyzing rare and sometimes not so rare adverse events [8–10]. Registries can provide large numbers of patients, but treatment decisions do not follow a uniform protocol and data must be analyzed retrospectively [11–16].

Biologics for Treatment of JIA

Etanercept is approved for treatment of polyarticular JIA in patients older than 2 years, including those with extended oligoarthritis, and psoriatic arthritis and enthesitis-related arthritis in patients older than 12 years. Adalimumab is approved for treating juvenile polyarthritis in children older than 2 years and enthesitis-related JIA in those older than 6 years. Abatacept is approved for polyarticular JIA patients older than 6 years if previous treatment with TNF inhibitors has failed. Tocilizumab is approved for treatment of polyarticular JIA, as well as systemic JIA (sJIA), in patients 2 years and older [36, 37], whereas canakinumab is approved only for children older than 2 years with systemic-onset JIA [17].

Because the availability of biologics for children is limited relative to adults, experience with unapproved biologics has been gained in children with refractory disease. Infliximab, a chimeric monoclonal antibody to TNF, is not approved for JIA but is approved for numerous diseases, including chronic inflammatory bowel disease in children [17]. Recently, golimumab, a human monoclonal anti-TNF antibody, was used in a clinical trial in polyarticular JIA [18]. Although anakinra, a natural IL-1 receptor antagonist, is not approved for treating JIA, it has shown efficacy and thus is recommended for sJIA patients [1].

Etanercept

Etanercept was the first TNF inhibitor to be approved for treating JIA, after it proved effective in a single placebo-controlled trial [3]. In this study, 69 children with polyarticular juvenile rheumatoid arthritis, a term used before the newer International League of Associations for Rheumatology (ILAR) classifications, received etanercept until week 12. Thereafter, 51 patients (74 %) were randomly assigned to receive either placebo or etanercept for up to 16 weeks. During the 12-week open-label study period, common infections were observed, including upper respiratory tract infections in 35 % of patients. Information on the occurrence of infections in the 4-month double-blind study is fair. No significant differences were reported in the frequency of adverse events between patients who received etanercept and those who received placebo. Fifty-eight patients entered the open-label extension and were observed for up to 8 years [8, 9]. The most commonly reported infections were upper respiratory tract infection, pharyngitis, skin infection, flu syndrome, otitis, and conjunctivitis. No significant increases were observed in the overall rates of adverse events or infections with prolonged exposure to etanercept. Six of nine serious adverse events (SAEs) leading to hospitalization were infectious events: peritonitis/appendicitis, aseptic meningitis associated with varicella-zoster virus infection, soft tissue infection, postoperative wound infection, dental abscess, and sepsis in a patient who received corticosteroids and methotrexate in parallel.

In the CLIPPER trial, which extended the JIA categories to oligoarticular JIA, enthesitis-related arthritis, and psoriatic arthritis, 127 patients received open-label etanercept for 12 weeks [7]. Fifty-eight patients (45.7 %) reported infections (198/100 person-years (PY)), three of which were serious, with one case each of gastroenteritis, bronchopneumonia, and pyelocystitis. In Trial of Early Aggressive Therapy (TREAT), 85 patients were randomly assigned to receive methotrexate, etanercept, and prednisolone or methotrexate and two placebos [19]. Fifty-one infections were reported, 18 of which occurred during methotrexate monotherapy (87/100 PY), 16 during combination therapy with methotrexate and etanercept (65/100 PY), and 17 during combination therapy with methotrexate, etanercept, and prednisolone (57/100 PY). Upper respiratory tract infections were common in both studies, followed by gastrointestinal infections (up to 19 %). One patient had a gastroenteritis/flu-like disease and was hospitalized. Two serious infections occurred in the TREAT study (pneumonia, septic hip arthritis), but both were resolved. The study patients were followed up for additional 2 years [20], during which four patients had six infections requiring systemic antibiotics; no cases of pneumonia occurred. There have been no cases of tuberculosis or other opportunistic infections in clinical trials performed with etanercept.

Several national registries provide far greater numbers of patients treated with etanercept. Since 1999, Dutch JIA patients, in whom etanercept use was approved by an evaluation board, have been included in a national survey [14]. Data have been reported from 146 patients, with a median follow-up of 2.5 years per patient (total follow-up 436 PY). In a registry study from the USA, 397 JIA patients were treated with etanercept or etanercept plus methotrexate over a 36-month period [16]; 197 patients on methotrexate alone served as the control group. Rates of medically important infections in the etanercept cohorts (1.8 and 2.1/100 PY) were higher than that in the methotrexate cohort (1.3/100 PY). Two cases of herpes zoster were reported.

The British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study analyzed medically significant infections in patients with JIA treated with etanercept and found a 2.1-fold increased rate in patients treated with etanercept compared with those treated with methotrexate after adjusting for potential confounding effects of baseline differences between the cohorts [15]. Parameters used for adjustment were baseline Childhood Health Assessment Questionnaire and Juvenile Arthritis Disease Activity Score (JADAS), disease duration, baseline oral steroid use, and ILAR JIA category. There were 184 medically significant infections (158 with etanercept and 26 with methotrexate), with an overall incidence of 4.8/100 PY (95 %

confidence interval (CI)=4.0, 5.6). The most common medically significant infections included primary varicella as well as zoster and respiratory tract infections. Within the etanercept cohort, patients on monotherapy had an incidence rate of 4.3/100 PY (95 % CI=3.2, 5.7) compared with 7.2/100 PY (95 % CI=5.4, 9.3) in the group receiving combination therapy with methotrexate. In addition, 64 first serious infections were reported, with 46 occurring with etanercept (22 with monotherapy and 24 with combination therapy), with a rate of 2.2/100 PY (95 % CI=1.6, 3.0). The most common serious infections reported were varicella and pneumonia. There was no difference in the rate of first serious infections across the cohorts. A Polish registry of 188 JIA patients [21] reported 16 cases of severe respiratory tract infections (4/100 PY) and, of note, the only case of tuberculosis (plus cytomegalovirus infection) so far in a JIA patient receiving etanercept.

The German BIKER (Biologika in der Kinderrheumatologie) registry recruited 2000 patients treated with etanercept for 4199 PY until December 31, 2014 (http://biker-register.de/index.php?page=jahresberichte) [11–13]. For comparison, a control cohort was set up to include patients not exposed to a biologic, including 1517 patients starting treatment with methotrexate. In the etanercept group, 341 infections were reported, compared with 281 infections in the control group. Among these, 26 serious infections in 24 patients were collected: 14 bacterial, 10 viral, and 2 of unknown type. Five infections occurred in patients receiving methotrexate monotherapy and 21 in those on etanercept. Rates of serious infection were 0.98/100 PY (95 % CI=0.6–1.6) in the etanercept/methotrexate combination therapy group and 0.52/100 PY (95 % CI=0.22–1.25) in the etanercept monotherapy group and were lowest in the methotrexate group (0.16/100 PY; 95 % CI=0.07–0.38). There was a statistically significant difference in rates between the etanercept and methotrexate groups, favoring methotrexate. Univariate analysis revealed several parameters that had a significant influence on the rate of serious infections, including a disease duration >2 years before the start of therapy, pretherapy with steroids as well as concomitant steroids at baseline, more than one nonbiologic disease-modifying antirheumatic drug used previously, a higher score on the 10-point JADAS (JADAS10) at baseline, and a higher mean JADAS10 score during the observation period. By multivariate analysis, only treatment with etanercept and the mean JADAS10 level during observation time remained significant. No case of tuberculosis or other opportunistic infections was reported, whereas 18 patients (0.4/100 PY) had at least one case of herpes zoster, which was significantly more frequent than in the nonbiologic control cohort, in which five events occurred (0.2/100 PY) [22].

Adalimumab

The effectiveness of adalimumab as monotherapy, as well as in combination with methotrexate, was demonstrated in a double-blind controlled study of polyarticular JIA in 171 patients [6]. Initially, all patients received adalimumab for 16 weeks; then, in a double-blind withdrawal study phase, the patients were randomly assigned to receive either adalimumab or placebo until week 48, followed by open-label treatment with adalimumab during a 104-week extension study. Seven serious infections (2.2/100 PY) were observed, but there were no cases of opportunistic infection or tuberculosis. In two small double-blind, placebo-controlled, head-to-head studies, 32 patients with juvenile ankylosing spondylitis and 46 patients with enthesitis-related arthritis were randomly treated with adalimumab or placebo [23, 24]. Infection rates in the adalimumab group were similar to those in the placebo group in both studies. In the first study, one serious infection (appendicitis) was observed during the double-blind study phase in the adalimumab group and two (gastroenteritis and pyelonephritis) in the open-label study phase in the adalimumab group. Thus, in total, three serious infections occurred in 14.8 treatment years (20.27/100 PY). In the second study, appendicitis was the only serious infection (rate=2.3/100 PY). Furthermore, adalimumab was studied in very young children with polyarticular JIA aged 2 to 4 years or weighed <15 kg [25]. Twenty-five infections—nasopharyngitis (n=8), fever (n=7), bronchitis, cough, rhinorrhea, and upper respiratory infections (n=6 each)—were reported. Three serious infections (gastroenteritis, rotavirus infection, varicella) were reported, but there were no opportunistic infections.

The long-term safety of adalimumab in patients with moderately to severely active polyarticular-course JIA who are prescribed and treated with adalimumab in routine clinical practice is being evaluated in an ongoing registry (STRIVE, www.clin.trials.gov). A 5-year interim analysis of 842 patients (540 in the adalimumab arm/302 in the methotrexate arm) revealed 13 patients (2.4 %) with serious infections (including abdominal abscess, acute tonsillitis, appendicitis, cellulitis, gastroenteritis, mononucleosis, viral meningitis, pneumonia, pyelonephritis, scarlet fever, subcutaneous abscess, tonsillitis, urinary tract infection, and varicella). Infection rates were similar in the methotrexate (15.4/100 PY) and adalimumab (12.1/100 PY) groups. The same results were observed with regard to serious infections [11 events in the methotrexate arm (1.4/100 PY) and 15 in the adalimumab arm (1.2/100 PY)] [26]. An interim analysis of the BIKER registry reported 289 JIA patients treated with adalimumab as of December 2012, for a total of 435.7 PY [27]. During this period, 75 infections occurred (25.9 %; rate=17/100 PY), one of which was classified as serious (urinary tract infection; rate=0.2/100 PY). More actual data from 552 patients with 679 years on treatment as

of December 2014 revealed comparable data, with 126 infections (22.8 %; rate=18.6/100 PY) and 5 serious infections (1 %; 0.74/100 PY). Zoster was reported in three patients.

Infliximab

Although a double-blind controlled, randomized study of infliximab was performed in 122 patients with polyarticular JIA, this agent is not approved for treatment of JIA. Infliximab at a dosage of 3 mg/kg body weight in combination with methotrexate was compared with treatment with placebo and methotrexate (on weeks 0, 2, 6, and 14) followed by infliximab dosed at 6 mg/kg body weight until week 52 [5]. Twenty-eight infections (1.67/100 PY) occurred in the placebo group compared with 41 (0.68/YR) in the 3 mg/kg infliximab group and 37 (0.89/100 PY) in the 6 mg/kg infliximab group. Upper respiratory tract infections were the most commonly reported. Three patients in the 3 mg/kg infliximab group had potential opportunistic infections: two with moniliasis and one with herpes zoster. Two SAE infections were reported in the placebo group (3.3 % of patients) compared with five in the 3 mg/kg infliximab (8.3 %) and one in the 6 mg/kg infliximab group (1.8 %); four cases of pneumonia occurred. The patients were followed up in an open-label extension study until week 204 [10]. Fifty-seven infections were reported, the most frequent being upper respiratory tract infections (25), pharyngitis (23), and rhinitis (12). Two serious infections (pneumonias) occurred, and one patient with asymptomatic tuberculosis (reported as pulmonary infiltration) was identified by repeated screening with negative mycobacterial cultures. This patient received quadruple antituberculosis therapy with cessation of infliximab and reached full resolution of the interstitial infiltrates.

In an open-label trial with 60 patients with polyarticular JIA, patients were assigned to treatment with infliximab plus methotrexate, methotrexate alone, or a combination of methotrexate, sulfasalazine, and hydroxychloroquine [28]. Thirty-six infections (1.7/100 PY) were observed in the infliximab group, 48 (2.8/100 PY) in the methotrexate group, and 35 (1.8/100 PY) in the combination therapy group. Upper respiratory tract infections and gastroenteritis were the most common infections, all occurring at comparable frequencies in the treatment groups. Four herpes infections, three of which required hospitalization, occurred in the methotrexate-only cohort. In a retrospective analysis including 82 JIA patients, viral infections (mostly upper respiratory tract infections) or bacterial infections requiring antibiotic therapy were reported in 50 patients (61 %). Four patients were hospitalized for severe infection (one each with bacterial superinfection of varicella, septic shock, fever of unknown origin, and perityphlitic abscess). One patient died from meningococcal sepsis [29]. Infliximab is approved for treatment of chronic inflammatory bowel disease in children at least 6 years of age [30]. In one study, 112 patients with pediatric Crohn's disease received infliximab 5 mg/kg at weeks 0, 2, and 6; thereafter, they were randomly assigned to receive infliximab 5 mg/kg (n=53) every 8 weeks or every 12 weeks (n=50); nine patients were not assigned. In total, 61 infections and 9 serious infections were observed, including colitis, pneumonia, furunculosis, adenitis, abscess, and enterocolitis; however, most were judged to be related to Crohn's disease. Pneumonia, occurring in three patients, and herpes zoster, in two patients, were the notable infections. Infections in pediatric patients with inflammatory bowel disease treated with TNF blockers were systematically reviewed, including 1407 patients treated with infliximab and 241 treated with adalimumab [31]. Most of the infections were mild. The list of serious infections included sepsis or bacteremia (n=10), meningitis (n=2), abdominal abscess (n=6), cellulitis (n=8), varicella (n=3), and several fungal infections (histoplasmosis, n=6; aspergillosis, n=1; pneumocystis pneumonia, n=1; candidemia, n=1). Four patients died.

Golimumab

Golimumab is a fully human monoclonal antibody targeting TNF-α. Results were presented from the GO-KIDS study, a randomized withdrawal trial in polyarticular JIA patients (n=173) aged 2 to <18 years [18]. During the first 16 weeks of the study, all patients received golimumab plus methotrexate; 76 patients received placebo from weeks 16 to 48, and 78 continued with golimumab. Two serious infections occurred during the open-label study phase, three in the golimumab group before week 48, and seven in the extension study from weeks 48 to 168, whereas no serious infections occurred in the placebo patients.

Abatacept

During the first 4 months of the open-label study phase, 190 patients with polyarticular JIA received abatacept; 68 infections were noted, mostly upper respiratory drug infections and viral infections [32]. During the double-blind study period, 27 infections occurred in the placebo group and 27 in the abatacept group. No serious or opportunistic infections were observed during the double-blind study phase. In the extension study, six serious infections were reported in five patients (1.3/100 PY; dengue fever, erysipelas, gastroenteritis, herpes zoster, bacterial meningitis, pyelonephritis) [33]. Pneumonia developed in three patients.

Tocilizumab

Tocilizumab, a monoclonal antibody against the IL-6 receptor, is applied intravenously in 4-week intervals at a dosage of 8 mg/kg in children weighing at least 30 kg and 10 mg/kg in those <30 kg. Children with sJIA receive tocilizumab in 2-

week intervals, with those weighing <30 kg receiving a dosage of 12 mg/kg. The first placebo-controlled trial using tocilizumab was performed in a withdrawal study in 56 Japanese sJIA patients. The patients received tocilizumab 8 mg/kg followed by up to six doses of either tocilizumab or placebo during the 12-week double-blind study phase [34]. Two serious infections were noted: one patient developed a macrophage activation syndrome (MAS)-like illness upon infectious mononucleosis; the other patient had herpes zoster during placebo administration in the double-blind study phase when serum tocilizumab concentrations were below the limit of quantification. Fifty patients were enrolled in a consecutive open-label extension study for up to 48 weeks [35]. Here, the most common infections were nasopharyngitis (n=33), upper respiratory tract infection (n=19), gastroenteritis (n=16), and bronchitis (n=14). Four serious infections were noted: bronchitis (n=2) and gastroenteritis (n=2).

In another placebo-controlled, double-blind trial, 112 sJIA patients were randomly assigned to receive either tocilizumab or placebo for a 12-week period (TENDER trial) [36]. More infections were observed in the tocilizumab group than in the placebo group (41 vs. 11 patients), with a comparable infection rate (3.4 vs. 2.9/100 PY). During the double-blind study phase, two serious infections occurred in the tocilizumab group only. Including the extension phase, a total of 18 serious infections occurred (11/100 PY), with five primary varicella infections, two cases of herpes zoster, four pneumonias, four upper respiratory tract infections, and five cases of gastroenteritis or gastritis. One patient developed laboratory anomalies consistent with mild MAS after varicella infection. Neutropenia was noted in 19 patients but was not associated with an increased infection risk. One patient died from probable streptococcal sepsis. Opportunistic infections and tuberculosis were not reported. In summary, infections, neutropenias, and the occurrence of infection-associated MAS are major safety concerns. Of importance, C-reactive protein (CRP) may not increase in patients treated with tocilizumab and the fever responses may be blunted even during serious bacterial infections, making the diagnosis difficult.

In a multinational, randomized, controlled withdrawal trial (CHERISH), 188 patients with polyarticular JIA received open-label tocilizumab for 16 weeks and placebo or tocilizumab for another 24 weeks [37]. During this study, 103 infections (55.9/100 PY) occurred, nine of which were serious (4.9/100 PY), including pneumonia (n=4), bronchitis (n=2), and cellulitis (n=2). A single serious infection (pneumonia) occurred in the tocilizumab group during the randomized study part.

Registry data from Japan on 417 pediatric patients with sJIA starting tocilizumab, with 407 PY, revealed 284 infections in 171 patients (69.8/100 PY) and 74 serious infections in 55 patients (18.2/100 PY) [38]. The most common serious infections were bacterial pneumonia (n=12, 2.9/100 PY), gastroenteritis (n=9, 2.2/100 PY), and bronchitis (n=6, 1.5/100 PY). There were three cases each of cellulitis, sepsis, herpes zoster, and influenza. Notably, two cases of *Pneumocystis jirovecii* pneumonia occurred. There were two deaths, one due to *Pseudomonas* infection leading to interstitial lung disease and sepsis. Furthermore, seven events of MAS occurred, two related to Epstein–Barr virus (EBV) reactivation. The rate of serious infections in clinical practice was higher than previously reported from trials.

The first results by the German BIKER registry of long-term safety surveillance in clinical practice reported 45 infections, 3 of which were serious, in 139 patients receiving tocilizumab (http://biker-register.de/index.php?page=jahresberichte). The serious infections included one case each of herpes zoster, appendicitis, and pneumonia. The rate of serious infections (2.2/100 PY) was significantly higher among the tocilizumab patients than the BIKER control group of nonbiologic-treated patients (risk ratio (RR)=6.1, 95 % CI=1.7–21.8, P=0.006).

Canakinumab

The IL-1β-specific long-acting antibody was studied in two consecutive trials involving 84 and 177 sJIA patients [39]. In study 1, 13 of 43 patients (30 %) receiving canakinumab had an infectious event, 2 (5 %) with a serious infection, compared with 5 patients (12 %) with an infection and 1 (2 %) with a serious infection in the placebo group. During the open-label part of study 2, 97 patients (55 %) had an infection and 7 (4 %) had a serious infection. During the second double-blind study phase, 27 patients (54 %) receiving canakinumab and 19 (38 %) on placebo had an infection and 2 patients in each group had a serious infection. One patient in the placebo group died from urosepsis; another patient died from MAS occurring in the context of a previous adenoviral infection. In summary, infections seem more frequent with canakinumab than with placebo.

Anakinra

The IL-1 receptor antagonist anakinra was first studied in 86 patients with polyarticular-course JIA [40]. One serious infection was reported in the open-label study phase; no serious infections were reported during the double-blind study phase. In the extension study, 16 patients (36 %) had an infectious episode; one event (hepatitis due to cytomegalovirus infection) was considered serious. Treatment with anakinra also has been reported in sJIA in open-label trials or retrospective case series [41]. Of 35 patients, one developed a visceral *Leishmania* infection. Other infections reported include varicella, rhinopharyngitis, labial herpes, bronchitis, and uncomplicated hepatitis A. The experience from France recently was updated in 189 patients, including 27 patients with sJIA and

35 patients with adult-onset Still's disease [42]. There were eight serious infections in adults and four in children (MAS and EBV infection, MAS and hepatitis, MAS and leishmaniasis, and scarlet fever). In a retrospective analysis of 46 JIA patients, bacterial infections were noted in two patients and hepatitis in one patient. One case of pneumococcal septicemia was noted in a 4-year-old child. A 3-year-old child developed pneumonia [43].

Population-Based Observational Experience

Analysis of national US Medicaid data has enabled the largest analysis by far of infections, using hospitalized bacterial infections as a criterion [44]. A total of 8479 JIA patients followed up for 13,003 PY were identified, including a group of patients treated with etanercept, adalimumab, and infliximab (16 %) as well as a group treated with methotrexate without a biologic (36 %). The remainder served as JIA controls. The addition of patients with nonimmunologic disease enabled comparison of infection rates in JIA patients. The most frequently observed infections were upper respiratory tract infections and pneumonia followed by septicemia and urinary tract infections. The spectrum of infections was comparable in both the JIA and non-JIA patients. Compared with non-JIA patients, JIA patients not treated with either methotrexate or TNF blockers had a twofold increased infection rate (95 % CI=1.5–2.5). The infection rate for patients treated with TNF inhibitors (3.5/100 PY; 95 % CI=2.6–4.5) or methotrexate (3.3/100 PY; 95 % CI=2.7–4.0) was similar to that for patients not receiving methotrexate or TNF inhibitors (2.5/100 PY; 95 % CI=2.2–2.9). Higher rates of hospitalized bacterial infection were observed in patients receiving steroids at dosages >10 mg/day (up to 7.3/100 PY in patients without concurrent methotrexate or TNF inhibitor use).

Discussion

Despite growing evidence regarding the efficacy and safety of an increasing number of biologics, it remains unclear whether these agents increase the risk of infections and which types of infections predominantly occur. Experience from clinical trials often is limited because of low patient numbers and a predefined short study period. Furthermore, these studies mostly use a withdrawal design. All patients initially are exposed to the drug before they enter the placebo-controlled study phase. Placebo usually is given until a disease flare occurs, when the patient is again placed on active treatment, limiting the duration of the placebo observation phase as well as a direct comparison between patients treated with a biologic and those receiving placebo. Thus, these studies are underpowered for safety analysis and cannot detect and validate less frequent risks. Open-label extension studies and registries may partly overcome these problems with high patient numbers and long observation times but also have their limitations.

The occurrence and aggravation of infections are a major concern in the care of patients with immunologic disorders and probably are even more important to consider in patients receiving combination treatment with corticosteroids, conventional immunosuppressants, and biologics. According to data from Beukelman et al. [33], patients with JIA already are at greater risk for bacterial infections leading to hospitalization than controls without an immunologic disease, even without receiving any medication. Hospitalization is the major indicator for seriousness; thus, comparison with data gained from clinical trials regarding serious infection rates seems reasonable. In contrast to other analyses, despite the use of corticosteroids, Beukelman et al. demonstrated no impact from the use of TNF inhibitors or methotrexate or their combination.

Data from clinical trials, and moreover data from registries, suggest that the risk of serious infection indeed is higher in patients receiving a biologic (with or without concomitant treatment with methotrexate) than in those receiving methotrexate only. As summarized in Table 1, the incidence of serious infections mostly was low throughout all the clinical trials performed in JIA patients. The rates varied from 2.8 to 10/100 PY in patients receiving etanercept, 2.2 to 20/100 PY with adalimumab, and 1.7 to 6.1/100 PY with infliximab, whereas the rate was 3/100 PY with golimumab and 4.9 to 13.2/100 PY with tocilizumab. The serious infection rate with abatacept was low (1.3/100 PY).

High patient numbers and long observation periods are clear advantages of the national registries and postmarketing studies. In some of the registries, the rate of serious infection appears higher in patients receiving biologics than in patients treated with methotrexate. In a US postmarketing study, the rate of medically important infections with etanercept plus methotrexate or etanercept alone was higher than that in patients on methotrexate alone. In a British registry, etanercept patients showed an increase in the rate of medically important infections compared with patients treated with methotrexate, with an unadjusted hazard ratio of 1.46 for etanercept versus methotrexate, which increased to 2.13 after adjustment for potential confounders. In the German BIKER registry, the rate of serious infection in patients receiving etanercept and adalimumab exceeds that observed in patients on methotrexate therapy. The adjusted hazard ratio was 6.0 for etanercept and 7.3 for adalimumab. The STRIVE registry, however, reported comparable rates of serious infections for adalimumab and methotrexate. Thus, most of the data from registries point to an increased risk for infection in patients receiving biologics. Differences among the results of the registries are partly explained methodologically or by differences in concomitant medication. Interestingly, according to data from the German BIKER registry, the rate of serious

Table 1 Rates of serious infections in patients receiving biologics and methotrexate in clinical trials and registries

Drug	Study	Kind of study	Patients, *n*	Observation period, years	Serious infections, *n*	SI/100 PY	95 % CI
Etanercept	Lovell et al. [3, 8, 9]	CT, EX	69	318	9	2.83	1.47–5.44
	Horneff et al. [7]	CT	127	29.2	3	10.27	3.31–31.86
	Wallace et al. [19, 20]	CT, EX	85	54	2	3.70	0.93–14.81
	BIKER[a]	RG	2000	4199	21	0.50	0.33–0.77
	Prince et al. [14]	RG	146	312	4	1.28	0.48–3.42
	Davies et al. [15]	RG	852	2060	46	2.23	1.67–2.98
	Giannini et al. [16]	RG	397	859.3	17[b]	1.98	1.23–3.18
	Zuber et al. [21]	RG	188	393	3	0.76	0.25–2.37
Total			3864	8224.5	105	1.28	1.06–1.55
Adalimumab	Lovell et al. [6]	CT	171	319.3	7	2.19	1.05–4.60
	Kingsbury et al. [26]	CT	32	45.1	2	4.43	1.11–17.73
	Horneff et al. [24]	CT	32	14.8	3	20.27	6.54–62.9
	Burgos-Vargas et al. [24]	CT	46	≈43	1	2.33	0.33–16.51
	BIKER[a]	RG	552	678.5	5	0.74	0.31–1.71
	Horneff et al. [26]	RG	540	1226.8	15	1.22	0.74–2.03
Total			1373	2327.5	33	1.42	1.01–1.99
Infliximab	Ruperto et al. [5]	CT	122	≈99	6	6.06	2.72–13.49
	Ruperto et al. [10]	EX	78	114.1	2	1.75	0.44–7.01
	Tynjälä et al. [28]	CT	20	20.8	0	0.00	n.d.
Total			220	233.9	8	3.42	1.71–6.84
Golimumab	Brunner et al. [18]	CT	173	164.8	5	3.03	1.26–7.29
Tocilizumab	Yokota et al. [36]	CT	56	≈228	30	13.16	9.20–18.82
	Benedetti et al. [36]	CT	112	152	18	11.84	7.46–18.80
	Brunner et al. [37]	CT	188	184	9	4.89	2.55–9.40
	BIKER[a]	RG	139	132	3	2.27	0.73–7.05
Total			495	696	60	8.62	6.69–11.10
Abatacept	Ruperto and Lovell [34]	CT	190	≈88	0	0.00	n.d.
	Ruperto and Lovell [35]	EX	153	≈450	6	1.33	0.60–2.97
Total			343	538	6	1.33	0.50–2.48
Canakinumab	Ruperto et al. [39]	CT	177	Not provided	11	n.d.	n.d.
Anakinra	Ilowite et al. [40]	CT	86	Not provided	1	n.d.	n.d.
	Lequerre et al. [41]	SV	35	Not provided	n.a.	n.d.	n.d.
	Rossi-Semerano et al. [42]	SV	62	Not provided	12	n.d.	n.d.
	Nigrovic et al. [43]	SV	46	Not provided	2	n.d.	n.d.
Methotrexate	Giannini et al. [16]	RG	197	387.8	5	1.29	0.54–3.10
	Horneff et al. [26]	RG	302	863.9	11	1.27	0.71–2.30
	BIKER[a]	RG	1517	3099.8	5	0.16	0.07–0.39
	Davies et al. [15]	RG	260	746	13	1.74	0.9–3.0
Total			2276	5097.5	34	0.67	0.48–0.93

CT clinical trial, *EX* extension study, *RG* registry, *SV* survey, *n.d.* not determine

[a] Data as of December 31, 2014

[b] Medically important

infections was associated with disease activity as measured by the JADAS [45]. After adjustment for confounders, treatment with etanercept or adalimumab and the mean JADAS10 throughout the treatment period remained to be the only significant parameters.

Much less clinical experience exists regarding JIA patients treated with infliximab, golimumab, abatacept, or tocilizumab. Rates of serious infections in clinical trials with tocilizumab ranged from 4.9 to 13.1 and appear higher compared with the rates in clinical trials of etanercept and adalimumab.

However, the rates were higher in sJIA patients treated with tocilizumab than in polyarticular JIA patients, which might be a result of the higher disease burden, as well as a greater need for concomitant treatment with corticosteroids, in sJIA patients but may also be a result of the higher tocilizumab dosage used or the shorter application interval of 2 weeks instead of 4 weeks [36, 37].

Data from both clinical trials and registries reveal a significantly increased risk for patients receiving any of the biologics—etanercept, adalimumab, infliximab, golimumab, and tocilizumab—compared with patients exposed to methotrexate only. Although abatacept appears to be an exception, the total patient number so far seems too low for a final judgment (Table 2).

Although serious infections were observed in all clinical trials and registry cohorts, opportunistic infections were rare. For example, tuberculosis is a major concern in adult patients treated with TNF inhibitors. Although screening strategies limit the risk of tuberculosis being activated, primary infection or reactivation occurred in a single JIA patient exposed to infliximab, who developed tuberculosis inside several clinical trials [8]. Registries covering several thousand JIA patients reported a single tuberculosis case from Poland. So far, no case has been reported from Germany, which may simply reflect the lower incidence of tuberculosis in Western Europe compared with Eastern Europe. With regard to tocilizumab, two cases of *P. jirovecii* pneumonia have been observed in children with sJIA. Furthermore, infections occurring in these susceptible patients may lead to MAS, a potentially fatal complication. The occurrence of herpes zoster during treatment with biologics has been described as a risk factor in adults with rheumatoid arthritis receiving TNF inhibitors [46]. Compared with patients with JIA treated with methotrexate, those receiving etanercept had a higher incidence of herpes zoster. However, although a generally higher herpes zoster rate was observed in JIA patients treated with etanercept, no serious or refractory manifestations occurred [47]. Other opportunistic infections appear to be of no importance.

Table 2 Univariate rate ratios of serious infections in patients treated with biologics compared with patients treated with methotrexate (pooled patient cohorts)

		RR	95 % CI	P^b
Methotrexate	0.67 (0.48–0.93)	Comparator		
Etanercept	1.28 (1.06–1.55)	1.91	1.30–2.82	0.00065
Adalimumab	1.42 (1.01–1.99)	2.13	11.32–3.43	0.002
Infliximab	3.42 (1.71–6.84)	5.13	2.37–11.08	0.00003
Golimumab	3.03 (1.26–7.29)	4.55	1.78–11.63	0.0016
Tocilizumab	8.62 (6.69–11.10)	12.92	8.49–19.68	<0.00001
Abatacept	1.33 (0.50–2.48)	1.67	0.70–3.98	0.246

Pooled data from Table 1

RR risk ratio

[b] Wald test

For early detection of medically important infections, patient information and regular clinical investigation are highly recommended, including analyses of blood cell counts and CRP. Vaccination strategies to prevent serious infections in susceptible patients seem reasonable. First, a review and updating of the patient's vaccination status should be performed according to national guidelines, with special consideration given to the varicella vaccine, a routine vaccination given in early life in many countries. Careful tuberculosis screening and routine retesting for tuberculosis appear valuable in patients at risk, because tuberculosis reactivation in JIA patients treated with anti-TNF antibodies has been described. Tapering corticosteroid dosages, or discontinuing steroids if improvement is seen, also may be recommended. According to guidelines of the Childhood Arthritis and Rheumatology Research Alliance (CARRA), tapering of methotrexate and even biologics also may be considered in patients with stable remission.

Conclusions

The safety profiles of biologics appear to be acceptable according to experience from the original trials, their long-term extension phases, and several national registries. Encouragingly, the number of serious infections has been relatively low; however, current knowledge clearly points to an increased risk of infection with biologics compared with methotrexate, although a differential analysis of the individual biologics suggests a lower risk for abatacept, adalimumab, and etanercept. The tolerability of tocilizumab appears to be limited because of the higher infection risk it carries, including the occurrence of opportunistic infections. These statements, however, are preliminary because of numerous confounders. Nevertheless, whether the underlying disease, concomitant treatment, or treatment with biologics is the cause, vigilance is required to prevent infections as well as secondary autoimmune diseases, cytopenias, and malignancies.

Compliance with Ethics Guidelines

Conflict of Interest Gerd Horneff declares the receipt of research grants from AbbVie, Pfizer, and Roche and speaker's fees from AbbVie, Novartis, Pfizer, and Roche.

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