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Recent advances in the use of Anti-TNFα therapy for the treatment of juvenile idiopathic arthritis

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Summary

Juvenile idiopathic arthritis (JIA) encompasses a group of diseases of unknown etiology having in common arthritis in at least 1 joint that persists for 6 weeks and begins before 16 years of age, with other conditions excluded. With a prevalence of 1 per 1,000 children in the USA, JIA is the most common pediatric rheumatic illness and a major cause of acquired childhood disability. During the last 20 years, the advent of host immune response modifiers known as biologic agents, in particular the anti-TNFα agents (etanercept, infliximab, adalimumab), which directly inhibit the action of pro-inflammatory mediators, has revolutionized the treatment and the expected outcome of JIA. This article highlights treatment indications of anti-TNFα drugs and their more frequent side effects in JIA patients.

Key words: Juvenile Idiopathic Arthritis**,** Etanercept**,** Infliximab**,** Adalimumab**,** Anti-TNFα agents**,** Side effects

Anti-TNFα treatment in JIA

Juvenile Idiopathic Arthritis (JIA) is the most common chronic rheumatic disease in childhood and may cause of disability and long-term impairment. JIA is not a single disease and encompasses different clinical conditions sharing an age of onset < 16 years and arthritis lasting at least six weeks.

Although nomenclature and classification need to be reconsidered, the most recent classification is based on the International League of Associations for Rheumatology (ILAR) Pediatric Task Force [1] which has divided the disease into the following different entities: Systemic JIA; Persistent Oligoarthritis; Extended Oligoarthritis; Rheumatoid Factor Negative Polyarthritis; Rheumatoid Factor Positive Polyarthritis; Psoriatic Arthritis; Enthesitis-Relatied Arthritis and Undifferentiated arthritis.

However, it is clear that systemic JIA, which encompasses about 10% of all JIA types, is a distinct clinical entity completely different from all the other forms. The high expression of pro-inflammatory cytokines in patients' sera [2], the presence of fever in all patients and the response to IL-1 or IL6 blockade [3,4] suggest that the disease might be considered an autoinflammatory disease, rather than an autoimmune disorder. Moreover, anti-TNFα treatment is not usually beneficial for patients with systemic JIA, suggesting again that these patients suffer from a different disease [5].

On the other hand, more than 70% of patients with JIA are affected by Oligo- or Polyarthritis and only these forms will be taken into account in this review.

Historically treatment has involved Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), systemic and Intra-Articular Corticosteroids, and Methotrexate. In the last decades therapeutic approaches for children with unremitting disease have included the use of drugs blocking TNFα. These treatments

have the capacity to suppress one of the main pro-inflammatory cytokine: TNFα, which is involved in systemic inflammation and many autoimmune disorders.

The more commonly used anti-TNFα agents include: Infliximab, a chimeric monoclonal antibody; Etanercept, a fusion protein; and Adalimumab, a fully human monoclonal antibody.

Infliximab and Etanercept seemed to provide a rapid and sustained reduction in disease activity in children with refractory JIA, but etanercept is usually still the first treatment choice among anti-TNFα drugs. Lovell et al. demonstrated, in fact, that treatment with Etanercept at the dose of 0.4 mg per kilogram twice weekly led to significant improvement in patients with active polyarticular JIA [6]. The same results were then confirmed by Kietz et al. on a smaller cohort of patients. The use of Etanercept showed to be safe and effective over a two and four year period [7].

It was also observed that the use of Etanercept in combination with Methotrexate, or other Disease Modifying Antirheumatic Drugs (DMARDs) was well tolerated and highly effective when compared with Etanercept alone, and years later Horneff et al. [8] also demonstrated that the combination therapy was more effective than monotherapy in achieving clinical remission.

Prince et al. firstly demonstrated that a single weekly double dose of Etanercept could be as effective as the twice weekly administration [9]; the same results were then confirmed by Horneff et al. in an elegant multicenter 12 week trial [10]. On the other hand, a higher dose of etanercept (>0,8 mg/kg twice weekly), even if considered safe and well tolerated did not seem to offer any additional benefit in those patients with inadequate response to standard dose.

The excellent clinical response to Etanercept, the safety profile of the drug and data suggesting a reduction in radiographic progression in JIA [11] have suggested to promote a trial with an early aggressive treatment characterized by two arms: the first with Methotrexate only, the second with a combination treatment including Methotrexate, Etanercept and Prednisone. However, there was no statistical difference between the two groups in achieving the primary end point (clinical remission at 6 months) [12]. The rate of clinical inactive disease at two years, among JIA patients treated with Etanercept, is about 50% [13].

Infliximab, although frequently used in Rheumatoid Arthritis, has not been widely employed in JIA. The first studies, however, reported a very low infliximab dosage (3-4 mg/kg) with weak clinical effectiveness; in the following years it has been suggested that the drug should have been used with a higher dosage (>6 mg/kg) in order to obtain significant results. In fact, Gerloni et al. demonstrated a good clinical response to Infliximab in combination with Methotrexate in patients who did not previously respond to Methotrexate treatment alone [14]. However these data were not later confirmed by an international, randomized multicenter placebo controlled double blind trial, that did not find any clinical difference between patients treated with Infliximab and those treated with placebo [15].

On the other hand Infliximab, as discussed in the next appropriate section, is very effective in JIA-related uveitis.

Anti-TNFα treatment seems to be particularly useful in those patients with Enthesitis Related Artthritis (ERA), a JIA subgroup corresponding to juvenile spondyloarthropathy and characterized by arthritis and enthesis, often associated with HLA-B27 positivity. In these patients both Infliximab and Etanercept seem to be effective. In particular, Etanercept has been recently associated to clinical remission in ERA patients [16] and Adalimumab has also been shown efficacious; their use is suggested for those patients who did not previously respond to DMARDs [17]. For inflammatory bowel disease-related arthritis infliximab seems to be the first choice.

Adalimumab is the relative more recent anti-TNFα biologic agent used in JIA. After the recognition of a possible role of Etanercept in uveitis development among patients with JIA [18], Adalimumab was firstly used in patients with JIA-related uveitis with good results [19]. Its efficacy in JIA was reported by Lovell et al. in a cohort of patients naive to treatment with other anti-TNFα agents [20], while Katsicas *et al.* showed good results in patients who already had failed another anti-TNFα agent [21]. According to the 2011 ACR recommendations, Adalimumab is suggested after failure of a first anti-TNFα drug, usually Etanercept, or as a first biologic DMARDs if uveitis is present [22];

however recently Adalimumab has been demonstrated safe and useful also as first biologic agent in JIA [23]

Despite the even larger use of biological treatment, data on their comparison are lacking.

Although Etanercept and Adalimumab are considered equally effective, in daily practice etanercept is most often prescribed while Adalimumab is mainly preferred when uveitis is present [24] even if patients with a history of uveitis presented higher risks for uveitis events while taking both etanercept and adalimumab in other reports [25]. In a recent systematic review, all available efficacy data from randomised controlled trials performed in JIA with biological agents were analysed, but indirect comparisons identified no significant differences in short-term efficacy [26]. Therefore, for now, paediatric rheumatologist has to rely on observational data and safety, practical and financial arguments. Head-to-head trials are still required to decide on the best biological treatment for JIA.

Side effects of anti-TNFα agents

The introduction of biologics in the treatment of patients with JIA have clearly revolutionized our approach to these disease and dramatically improved the outcome of affected children. Still, some concerns exist on the safety of these drugs, in particular regarding the long-term side effects, given the limited period of time since they have been introduced. The evaluation of long-term safety of anti-TNFα is of the utmost importance for rheumatologists, since a consistent part of children with JIA will enter adulthood with active disease and will need ongoing medical treatment [27]. Unfortunately, safety data on the use of these drugs in children come from very heterogeneous studies, in terms of population selected, ILAR category of the patients recruited, study design (i.e randomized controlled trials, retrospective cohort analysis, patients registries, case series and case reports), drug regimen, definition of adverse events and serious adverse events, and events reporting system. Furthermore, given the JIA prevalence, even the largest studies available in the literature may not have considered enough patients to catch rare events. These are very important biases to consider when trying to draw conclusions on the safety of these drugs in children with JIA [28].

From a theoretical point of view, concerns exist on the possible correlation between the anti-TNFα blockers and the occurrence of infections and tumors, given the functions of TNFα on the immune system [29]. Serious adverse events (SAEs) have been reported in 3-4% of patients during the first phases of RCTs, while longer term studies reported a wider variability in the incidence of SAEs, from 2 to more than 20 events/100 patients/year [6; 12; 15; 20; 30-42]. The more commonly reported SAEs are injection site and infusion reactions. Adverse Events (AEs) occurred in almost a third of the patients enrolled in the RCTs and were reported with an incidence from less than 50 cases/100patient/year to more than 2500 cases/100patients/year in other studies. The more commonly described AEs were local injection site reactions or infusion reactions and infections. Again, this very wide variability in the incidence of AEs and SAEs is probably caused by the extreme heterogeneity of the studies published, as already discussed. Table 1 reports a selection of studies with data on long-term safety of the anti-TNFα drugs.

Autoimmune disorders

Few reports focus on specific SAEs and AEs. Krishnan et al. evaluated the risk to develop inflammatory bowel disease (IBD) in patients receiving anti-TNFα for JIA or RA, reviewing the files from the Food and Drug Administration Adverse Event Reporting System. A total of 55 patients with JIA developed IBD: 50 patients were on Etanercept, 2 on Adalimumab and 3 on Infliximab. With the application of the Naranjo score, in the majority of cases the association between the drug and the IBD was considered "probable" [43,44]. Methodological biases hamper the strength of this study in determining a clear link between IBD and anti-TNFα therapy, and further studies may clarify if the development of IBD could be a possible "paradoxical reaction" in children with JIA treated with TNFα-blockers. Of note, it has been recently demonstrated in a large German JIA cohort that among patients treated with methotrexate (MTX) the IBD incidence was significantly lower compared with patients not treated with MTX, while Etanercept monotherapy (but not the combination of ETN and MTX) was associated with an increased incidence of IBD.

This indirectly suggests both a protective effect of MTX in IBD development of patients wuth JIA and possible effect in Etanercept in IBD incidence [45].

Infectious complications

Toussi et al. systematically reviewed the incidence of infections in children with JIA treated with anti-TNFα drugs: severe infections occurred in up to 9% of patients treated, with the respiratory tract and musculoskeletal system as the main sites of infections. Mild infections occurred more frequently, from 8% to 97% percent of patients, mainly in the upper respiratory tract. Even though the majority of studies considered failed to report the etiology of the infections, *Streptococcus pyogenes* and *Staphylococcus aureus* were the bacterial pathogens most often identified, while herpes simplex virus and varicella zoster virus were the most frequent among viral infections [46]. Very few cases of *M. tuberculosis* were described, probably thanks to the application of tuberculosis screening in all JIA patients prior to receiving a TNFα blocker. This screening was first recommended for adults with RA, and later applied also in children with JIA [22; 47]. Of note, annual screening of children at low risk of TB with an initial negative TB test is considered inappropriate (level D) [48].

Walters et al. prospectively followed for up to 12 months 56 JIA patients, 20 of whom received TNFα blockers, while the remaining 36 did not receive immunosuppressive therapy. There was no difference in the infection-rate between TNF and no-TNF receiving patients. Although this study was biased by the relatively low number of patients and a short follow-up, it suggests that patients with JIA may have an increased risk of infection, independently from the underlying therapy, compared to children without JIA [49-50].

Malignancy

The possible correlation between anti-TNFα treatment and the onset of tumors is the more relevant concern on the long-term safety of these drugs. Indeed, in the first reports tumors were rarely reported as SAEs. It was therefore worrisome that in 2008 the FDA issued a black box warning about the possible association between the use of anti-TNF agents in children and the development

of malignancies. This warning was the base of a study by Diak et al. published two years later, which identified through the FDA Adverse Reporting System 48 cases of malignancies among children with JIA or IBD receiving TNF blockers [51]. This report includes biases such as the combination of different diseases (i.e. JIA and IBD) and the lack of consideration of other concomitant immunosuppressant drugs. Moreover, no data were available at the time of publication on the background incidence of malignancy in patients with JIA. Beukelman *et al.* subsequently compared children with JIA, treated with methotrexate and/or an anti-TNFα, with children with attention deficit hyperactivity disorders. The authors found that children with JIA were at higher risk of developing malignancy, and this risk was not increased by the association of a TNFα blocker [52]. Similar results were obtained by Nordstrom *et al.*, who found that the incidence rates of cancer were respectively 67.0 and 23.2 cases/100,000 person-years for JIA and non-JIA children, with a 3-fold increased risk of malignancy in biologics-naïve JIA children, compared to non JIA children [53]. These studies seem therefore to suggest that JIA patients are at higher risk of developing cancer, independently from the anti-TNFα treatment. Given the low incidence of both JIA and malignancy in childhood, and the possible long delay between the onset of JIA and cancer, very large cohorts of patients should be followed for long periods before reaching firm conclusions. Still, pediatric rheumatologists should keep an active surveillance on their patients with JIA, on whatever treatment used, to early identify the development of malignancy.

JIA-related uveitis

The association between Juvenile Idiopathic Arthritis and ocular inflammation was firstly described by Ohm in 1910 and subsequently confirmed by several authors. Data regarding the incidence of uveitis in JIA (4–24%) differ considerably due to the recruitment of different medical centres and to geographical variations. A recent meta-analysis estimated worldwide incidence at about 8.3% [54]. To date, JIA-related uveitis represents the most common cause of pediatric uveitis in developed countries. Children affected by JIA who develop ocular involvement do so in up to 50% of cases within 3 months and in up to 90% within 4 years from the diagnosis. Only 2-7% of patients are

diagnosed with uveitis before the onset of arthritis. Ocular inflammation may also appear for the first time during adulthood. Children affected by uveitis may also present a severe articular involvement, however the presence of ocular inflammation does not seem to affect the long-term prognosis of joint involvement and the clinical course of the two conditions may be completely independent as well.

JIA-associated uveitis typically presents a non-granulomatous bilateral involvement with chronic course. Anterior chamber is primarily affected, isolated or in the context of panuveitis, whereas posterior involvement alone is less common.

Considering patients affected by JIA and according to ILAR, an ophthalmologic evaluation should be performed at the time of diagnosis and periodically repeated regardless of presence or absence of symptoms. The frequency of ocular examination is defined on the basis of the subtype of arthritis, the age at onset and the presence of ANA.

Compared to adults, childhood uveitis is characterized by poor prognosis and higher risk of secondary complications, with considerable socioeconomic burden. Even if the uveitis remission rate may be up to 70-80%, uveitis still represents the third leading cause of blindness in developed countries. Among children suffering from JIA, visual complications have been reported in up to 80% of patients after 3 years and in almost 100% of patients after 20 years of disease. These develop as a consequence of persistent or recurrent ocular inflammation, but also as result of chronic steroid treatment [55-56].

The most common complications include: cataract (19-81% of patients), glaucoma (8-38%), band keratopathy (7-10%), synechiae (8-75%), cystoid macular oedema (8-42%), ocular hypotony (19%), retinal detachment, retinal ischemia and optic atrophy [57]. Up to 30% of patients show reduced visual acuity and up to 10% develop blindness. From 28% to 70% of affected children may require surgical therapy.

Treatment for non-infectious uveitis is based on a “step-by-step” approach, in order to control local inflammation, achieve a corticosteroid-sparing effect and reduce the risk of visual complications

[58-59]. Local steroid therapy associated to mydriatics is proposed for mild-to-moderate conditions, especially in case of anterior involvement. Severe ocular inflammation may instead require oral or intravenous systemic steroid treatment.

In corticosteroid-resistant and corticosteroid-dependent cases systemic immunomodulatory agents should be considered. For patients intolerant or non-responders to methotrexate, biologic therapies represent a valid option.

Considering anti-TNFα treatments, the therapies approved for paediatric population comprise infliximab, etanercept and adalimumab. Despite presenting a similar mechanism of action, these molecules showed different efficacy in uveitis treatment. A recent meta-analysis highlighted a superior efficacy of Adalimumab and Infliximab when compared to Etanercept, which is not routinely recommended [59]. Infliximab represents an efficient short-term treatment for uveitis [60]. A retrospective clinical trial documented a significant resolution of ocular inflammation in 16 patients undergoing MTX and Infliximab evaluated at 3, 6, 9 and 12 months [61]. However, efficacy in long-term treatment seems to be limited, with subsequent possibility of ocular relapse [62-63].

If favorable outcomes have been reported for Etanercept in articular involvement, its effectiveness in ocular inflammation seems to be limited. Infliximab superiority on Etanercept was reported in adults affected by JIA-related uveitis [64]. A randomized controlled trial involving pediatric patients did not show significant difference between the administration of Etanercept and placebo. Therefore, Etanercept is not currently recommended as first systemic biologic therapy for uveitis [65].

On the other hand, several clinical trials suggested the efficacy of Adalimumab in the treatment of uveitis [19; 66]. We reported the superiority of Adalimumab compared to Infliximab in maintaining long-term ocular remission among 33 children affected by chronic uveitis [67]. This evidence has been confirmed by a following multicentre study involving 108 children affected by JIA-related arthritis. Both Infliximab and Adalimumab provided good safety and efficacy data, however

Adalimumab was more likely to achieve long-term remission, especially if administered as first TNFα inhibitor [68]. We also showed, even if limited to a relatively small group, a better efficacy of Adalimumab when used as first anti-TNFα treatment in childhood chronic uveitis. [69].

A recent meta-analysis provides evidence that, when a previous course of anti-TNFα failed to induce/maintain remission in chronic uveitis of children, switching to a new anti-TNFα treatment (Adalimumab and Infliximab) has a favorable effect in the improvement of intraocular inflammation [70].

Although not yet approved, Golimumab has been described as a promising new therapeutic option for severe uveitis in those patients who have not responded to other biologics [71]

Expert Commentary

JIA is one of the most common autoimmune disorders. In the last decades great improvements in disease control and sequelae prevention have been reached. This is due mostly to the use of anti-TNFα drugs. However, some aspects still remain to be clarified. The safety of anti-TNFα use has been demonstrated in the last years and the associated risk to develop autoimmune disorder, malignancy and infections appears now very low, at least in the short term.

The most common problem for clinicians dealing with JIA patients treated with anti-TNFα drugs is the possible loss of effect during time. This is probably due to the endogenous production of antibodies against anti-TNFα drugs, and sometimes the drug needs to be switched with another biologic.

It is also not still clear which anti-TNFα should be used first and which should be considered the best treatment for specific JIA subgroups. This is mostly due to the lack of comparative studies between anti-TNFα drugs among the same JIA subgroup of patients. Moreover the presence of newer biologics available on market does not allow a complete evaluation of all therapeutic strategies and, in the next years, the presence of biosimilars, with the same expected clinical but lower production costs, will probably modify the drug prescriptions and the list of approved indications.

Five-year view

JIA medical management has never been clearly and widely established; however in the last years expert guidelines for JIA treatment have been formulated [22]. The most relevant aspect was the fact that, despite some reports suggesting a better clinical effect of early aggressive treatment with biologics [12], the TNFα agents still remain in the second line treatment after failure of NSAIDs, corticosteroids injection where possible and Methotrexate treatment. Although early aggressive therapy for JIA may be an interesting strategy, published evidence so far is too weak to recommend this as a general accepted therapeutic strategy [72; 73]. It is also important to underline that a wide and non selective use of anti-TNFα agents could probably not be affordable for the national health systems.

Finding one or more predictive markers of response to anti-TNFα agents has a great importance in the clinical practice in order to identify a subset of patients with a higher chance of response, who could benefit from an early treatment. However these data are scarce at the moment so far. Until now, research studies for identification of treatment response markers were mostly aimed to evaluate the role of single nucleotide polymorphisms (SNPs) among genes involved in cytokine pharmacodynamics and pharmacokinetics.

Several studies have identified polymorphisms associated to anti-TNFα response, however no one of these markers reached an adequate level of evidence to be used in the clinical practice [74-76].

It is common to experience a progressive lack of effect of anti-TNFα treatments during time. This is probably due to the production of antibodies against anti-TNFα drugs which bind effector binding sites [77-78]. In order to avoid such a complication, some authors suggest to add a small dose of Methotrexate (usually 5 mg/week irrespectively of the body surface) with the goal to decrease autoantibody production; however, results are still debated.

Finally, another recent development is the presence on the market of biosimilars, biological medical products which are a copy of an original product that is manufactured by a different company. Biosimilars are a version of original biologic products, and can be manufactured when the original

product patent expires. They are now entering in the use of autoimmune chronic disorders, and their lower costs might probably improve their use in clinical settings. However it is not still demonstrated if their effectiveness is similar to the original products, and it is important to underline that they are not yet approved for JIA.

Key issues

- Juvenile Idiopathic Arthritis is one of the most common autoimmune diseases in childhood and is characterized by the onset < 16 years and presence of arthritis lasting more than 6 weeks.
- The use of biologic DMARDs, in particular the anti-TNFα agents, has increased in the last years, but their application is currently suggested only for patients who do not respond to first line treatment (NSAIDs, intra-articular corticosteroids, Methotrexate).
- Etanercept is usually the first treatment choice among biologic DMARDs, but Adalimumab represents an effective alternative.
- Anti-TNFα agents are safe, but a relatively higher risk of infections has been reported among patients on long term treatment; in particular potential reactivation of latent tuberculosis seems to be particularly threatening. For these reasons, attention should be made in ruling out latent tuberculosis before starting such treatments, and special attention during febrile infections should be given while receiving anti-TNFα treatments.
- Some reports suggest a particular association of anti-TNFα treatment with occurence of autoimmune diseases. In particular, a possible association between the use of etanercept and uveitis development has been suggested.
- Anti-TNFα treatment has been reported to be particular effective also in treating uveitis, the most common extra-articular complication of JIA.

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Reference annotations

** Of interest*
*** Of considerable interest*

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author	type of study	# of pts	main drug	duration of tx (range)	pts/yrs	other drugs	SAEs (per 100 pt/years)	Type of SAEs (per 100 pt/years)	AEs	Type of AEs	Comments
Lovell et al., 2008 [20]	open label RCT	171	ADA	16 wks	27,3*/29,3**	±MTX	3(10)*/ 4(10)**	3 RTI 1 g.i. infection 2 lab abnormalities 1 HSV infection 2 VZV infection 1 abdominal pain 1 hydrocefalus	422(1550)*/ 447(1530)**	902 injection-site reactions 157 URTI 74 viral infection	*+MTX/**noMTX
	double-blind withdrawal RCT			32 wks	23,3*/25**		1(10)*/0**		389(2310)*/ 324(2630)**		only AEs possibly related to study drug were reported
	open-label extension			NA	127,4*/102,6**		7(10)*/2**		694(540)*/ 581(570)**		
Ruperto et al., 2010 [35]	open label CT	78	INF	114,1	NA	plus MTX	17	6 worsening arthritis 2 pneumonia 2 infusion reaction 1 tubercolosis	71	URTI (>20% of patients) infusion reactions (25 patients) ANA and anti-DNA onset	
Tynjala et al., 2011 [30]	open-label RCT	20	INF	54 wks	20,8	plus MTX	NA	NA	100(48)	36(17) URTI 3(1) g.i. 14(7) lab abnormalities 2(1) infusion reaction	polyarticular JIA only
Zuber et al., 2011 [32]	national registry	188	ETA	72mths	393	DMARDs	6 (2)	optic disc oedema leukopenia MAS TBC+CMV infection	1162 (296)	RTI (24,8) HSV infection (9,7) gastroenteritis (8) urinary infection (5,1) meningitis (0,5) influenza (0,8) optic disc edema (4,3)	
Minden et al.,2012 [38]	national registry (JuMBO)	346	ETA	4.1 yrs (1-10)	598	DMARDs ±biologics	54 (9)	infections (1.7) 1 death for suicide 2IBD 2 psoriasis 4 uveitis	NA	NA	

								1 SLE 1 neuromyelitis			
Schmeling et al., 2014 [39]	national registry (BiKeR)	289 (130*,159**)	ADA	1,2 yrs (0,58-1,88)* 1,13 yrs (0,61-1,94)**	NA	DMARDs DMARDs ±biologics	6 (3,2)* 5 (2)**	1 Anxiety* 1 Urinary tract infection* 1 Diabetes Mellitus* 1 Concussion* 1 Nephritis* 1 Urticaria* 1 Paresthesia** 1 Abnormal lab** 1 Crohn's disease** 1 Intestinal resection**	112(59)* 110 (44,8)**	26*/18**Respiratory tract infection 4*/1** g.i. tract infection 13*/4 other infections 1* varicella 1** zoster 19*/13** g.i. complains 4*/4** injection site pain 5*/4** blod test abnormalities 2*/2** headache 1*/1** mood dysorder 11*/17**miscellaneous	* biologics-naive/** bilogic switchers
Klotsche et al., 2015 [42]	national registry (BiKeR+JuMBO)	1734(1414*,320**)	ETA*,ADA**		4461*/493**	DMARDs ±biologics	199 (4,5)*/23 (4,7)**	6 (0,09)*/2 (0,27)** malignancies 4 (0,06)* deaths (2 sepsis, one MAS, one carditis)	NA	255(5,72)*/56(11,36)** infections 21(0,5)*/1(0,2)** uveitis 12(0,27)*/1(0,2)** IBD 17(0,38)*/0** blood disorders	* ETA/**ADA
Windschall et al., 2015 [41]	national registry (BiKeR)	1374	ETA		2805,38	DMARDs ±biologics	108(21,13)	NA	762(142,02)	NA	
Tarkiainen et al., 2015 [40]	national registry	348	ETA*,INF**,ADA***	NA	710*/591**/188***	DMARDs ±biologics	213*/214**/94***	infections (3,9) labworks abnormalities (3,1) administration site reactions (0,9) neurologic/psychiatric disorders (0,9)	(169*/215**/167***)		*ETA/**INF/***ADA

Table 1: a selection of papers reporting on safety of antiTNF blockers, selected based on design of the study, number of patients recruited, year of publication (ETA: etanercept; INF: infliximab; ADA: adalimumab; DMARDs: disease-modifying anti-rheumatic drugs; MTX: methotrexate; U/RTI: upper/respiratory tract infections; IBD: inflammatory bowel disease)