Review

The risk of infections associated with rheumatoid arthritis, with its comorbidity and treatment

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Abstract

RA is known to be associated with an increased risk of serious infection. Even more than 50 years ago, observational studies showed a greater than 2-fold increased risk of serious infection in RA. This was reinforced by various subsequent cohort studies. The elevated susceptibility of patients with RA can be explained by the pathobiology of the disease itself, the impact of chronic comorbid conditions, as well as sequelae of immunosuppressive treatment. It has been suggested that premature ageing of the immune system in RA contributes to weakened protection against infectious organisms. In addition, chronic comorbid conditions such as diabetes or chronic lung or kidney disease, disease-related functional disability, as well as lifestyle factors such as smoking, increase the risk in individual patients. For a long time glucocorticoids (GCs) have been used as potent immunosuppressive drugs in RA. There is evidence that they increase the risk of serious infections up to 4-fold in a dose-dependent manner. TNF-α inhibitors increase the serious infection risk up to 2-fold. They have, however, the potential to outweigh their risk when higher GC doses can be tapered down. If patients need higher dosages of GCs in addition to treatment with biologic agents, their risk of infection is substantial. This combination should be used carefully and, if possible, avoided in patients with additional risk factors such as older age or comorbid conditions.

Key words: rheumatoid arthritis, serious infections, susceptibility, immunosuppressive drugs, glucocorticoids, TNF-α inhibitors, comorbidity.

Introduction

Serious infections are a major concern in patients with RA or other inflammatory rheumatic diseases and contribute to an increased overall mortality [1–9]. With the advent of TNF-α inhibitors for the treatment of RA, concerns regarding the infection risk were reinforced due to their specific mode of action, and infections as possible adverse outcomes were observed with greater attention. Therefore nearly all RCTs with TNF-α inhibitors reported incidence rates of serious infections during the double-blinded phases, which had not been the case in the earlier trials of conventional DMARDs. In addition, after licensing of the first TNF-α inhibitors, biologics registers were established

in various European countries with the aim of investigating their long-term safety under real-life conditions [10]. As a result of both developments, we have today a wealth of information on the infection risk of patients treated with biologics as well as with conventional DMARDs.

When considering the infection risk in RA, we have to take into account the interaction of various endogenous and exogenous risk factors: (i) RA itself as a chronic disorder with immunological dysfunctions, (ii) immuno-compromising comorbidities, as well as (iii) the use of potent immunomodulatory drugs. It is a methodological challenge to estimate the contribution of each of these risk factors to the overall infection risk in RA patients.

With this in mind, we will briefly review the infection risk reported for RA in the pre-biologic era, followed by a summary of the results of RCTs and observational studies with immunosuppressive drugs such as glucocorticoids (GCs) and TNF inhibitors. Our focus will be on the lessons we can learn from different kinds of studies and how we can transfer their results to individual patients in daily practice, taking into account that treatment is not the only risk factor of infectious complications and that risk profiles of individual patients may change over time. We will therefore

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differentiate between the infection risks observed in cohorts of patients and the risk of individual patients and describe what we gain from this differentiation.

Incidence of infectious diseases in patients with RA

Since the 1950s, observational studies evaluating overall prognosis and mortality in patients with RA have indicated a noticeable risk of infectious diseases developing in these patients [1, 11]. During the early period, RA was difficult to treat, and severe disease courses with persistent systemic inflammation led to joint damage, immobility and complications such as amyloidosis with subsequent renal failure. Later, surgical treatment of damaged joints was observed to be associated with a higher risk of complicating septic arthritis [12–14]. And even without surgical procedures, septicaemia as well as septic arthritis remain as major concerns in patients with inflammatory rheumatic diseases [6, 15–20]. In the following decades of the last century, controlled observational studies found that age-adjusted mortality in RA patients was about 2-fold increased compared with the general population and infectious diseases were one of the three leading causes of premature death in RA cohorts in the USA and in Europe [4, 6, 18, 20]. In a retrospective cohort study of incident RA cases with disease onset between 1955 and 1994, Doran *et al*. [21] found a high rate of infections requiring hospitalizations (9.6 infections/100 person-years) in 609 patients with established RA. This rate was almost 2-fold (hazard ratio 1.9; 95% CI 1.7, 2.1) higher than in 609 age- and sex-matched non-RA controls [21]. As well, Franklin *et al*. [17] showed in a prospective cohort of 2108 unselected patients with inflammatory polyarthritis in Norwich, UK, an increased infection risk of more than two-and-a-half times that of the general population. Similar results were found by Smitten *et al*. [22] for hospitalized infections. Concerning specific pathogens, in a retrospective cohort of RA patients hospitalized between 1963 and 1998, pneumococcal infection was found at more than 2-fold the rate, when compared with a cohort of patients with non-immune-mediated underlying diseases [23].

Is there higher susceptibility to infections in patients with RA due to alterations in the immune system?

Immunological considerations support a possible link between infection risk and alterations of the immune system in patients with inflammatory rheumatic diseases. Various disturbances of both the innate and adaptive immune system were thought to contribute to the increased infection risk in RA: first, neutropenia is common in RA patients with severe disease courses or under immunosuppressive treatments; increased pathological immune complexes or direct anti-neutrophil antibodies play a pivotal role in mediating the disease-associated phenomenon. Pathological immune complexes may cause functional

impairment, increased margination or enhanced apoptosis of neutrophils; deficits in the number and function of these first-line defence cells at the site of bacterial invasion and growth may be the consequence [24]. Secondly, adaptive cellular immunity is importantly impaired by a constricted TCR repertoire, which is crucial for naïve T lymphocytes to recognize all potential harmless and harmful antigens [25]. In addition, the capacity of clonal expansion of naïve T cells in response to a previously unknown antigen was significantly reduced in RA patients compared with healthy controls [26]. Frequencies of newly generated naïve T cells immigrating from the thymus into the periphery were shown to be age-inappropriately decreased in RA patients [26]. This was one of the first hints that premature ageing of the immune system in immune-mediated diseases such as RA may be responsible for damage to key immune functions, and therefore for weakened protection against infectious diseases [27, 28]. Further, a higher risk of RA patients to severe infections may be caused by specific gene polymorphisms, e.g. in the TRAF1/C5 locus [29], where complement factor 5 plays a well-known role in the innate immunity against infectious agents [30]. These findings suggest an increased susceptibility to infections in RA patients due to disease-related alterations of the immune system.

The impact of comorbid conditions, clinical status and lifestyle on infection risk

There is undoubtedly an influence of older age [31–33] and specific comorbid conditions on the infection risk in RA and other inflammatory rheumatic diseases. Significantly increased infection risks have been described for patients with chronic obstructive pulmonary disease and other chronic lung diseases [31, 34–38], chronic kidney diseases [31, 37] and diabetes mellitus [37, 38]. A considerable exogenous risk factor for the development of infections is smoking. It is linked to the pathogenesis of RA [39, 40] and at the same time is a risk factor for distinct infectious diseases [41].

Only limited evidence exists regarding the impact of the disease activity on the susceptibility for infections, possibly due to the close association of RA disease activity and (dosage of) immunosuppressive treatment. Au *et al*. [42] found higher rates of hospitalized infections in RA patients with moderate or high disease activity compared with those with low disease activity. Per 0.6 U in DAS28, they observed a significant, 1.3-fold increase in the risk of serious infection. As in the general population, functional limitations of patients with RA are associated with a greater risk of infections. This has been confirmed by several authors [31, 34, 35, 38, 42].

The impact of GC treatment

GCs are potent immunosuppressive drugs that are widely used in rheumatological care. Their potential to increase the susceptibility to major infections has been described

for several inflammatory rheumatic diseases [31, 43, 44] and is also seen in patients with other non-rheumatic diseases. By contrast, in a meta-analysis of RCTs investigating the efficacy of GCs, Dixon et al. [45] did not find higher infection rates in the GC treatment arms [relative risk (RR) 0.97; 95% CI 0.69, 1.39]. However, most of the trials had sample sizes of < 50 per treatment arm. Furthermore, in most of these trials the incidence of serious infections was not an event of interest and therefore was not reported by physicians in a standardized manner.

Reporting of infections ranged from the percentage of patients with influenza or bronchitis to the number of patients with infections that led to withdrawal of MTX. The inconsistent reporting and a marked heterogeneity between the trials prevented Dixon et al. [45] from drawing any definite conclusion [45]. Haraoui et al. [46] recently re-analysed the data of a large RCT on certolizumab pegol (n = 763) vs placebo (n = 199). They observed an increased risk of serious infections in patients who received GCs in doses of >5 up to 10 mg/day compared with those receiving no or <5 mg/day in both arms of the trial. A 2.5-fold increase in the incidence of serious infections was found in a review of anakinra RCTs when patients with and without GC use at baseline were compared [47].

This result is supported by a meta-analysis of observational studies. Dixon et al. [45] found a significantly increased risk for serious infections in patients treated with GCs, which was also dose dependent. For patients receiving <5 mg/day, the authors estimated an RR of 1.4 (1.2, 1.6), for 5–10 mg/day an RR of 1.9 (95% CI 1.7, 2.2) and for 10–20 mg/day an RR of 3.0 (1.9, 4.7). This dose-dependent increase in the infection risk was also observed in recently performed observational studies in RA [31, 42, 48, 49] that were not included in the meta-analysis of Dixon et al. It is further supported by the fact that the association between dosage and infection risk is clearly stronger for GCs the patient received at the time point of infection than for GCs received months or years earlier [50, 51].

Impact of cytokine inhibitors

TNF-α plays a crucial role in the host defence against bacterial and viral invasions. It mediates recruiting and activation of macrophages and thereby initiates responses of the innate immune system at infection sites. It is particularly essential for immune mechanisms against intracellular pathogens such as mycobacteria. This central immunological function of TNF-α in host defence has raised concerns about an increased risk of serious infections in patients treated with TNF-α-inhibiting agents.

Results of RCTs

In a meta-analysis of RCT data, Bongartz et al. [52] found a significant, 2-fold-increased risk of serious infections in RA patients receiving adalimumab or infliximab. The increase was slightly lower (1.8) when only low dosages were compared with placebo. In contrast to these findings, the meta-analysis of Leombruno et al. [53] and those of others [54, 55], which were performed later and included more RCTs, did not observe a significantly increased infection risk or observed the increase only in verum arms with high, non-recommended dosages of biologics [53]. Taking all results of meta-analyses together, the risk for serious infections in RA corresponds to an odds ratio (OR) of approximately 1.2–1.4 [53, 54] in anti-TNF-treated patients. Similar results were found for abatacept (OR = 1.4), rituximab (OR = 1.5) [55] and tocilizumab (OR = 1.3) [56]. For anakinra, incidence rates of 1.7 and 5.4 serious infections/100 patient-years, respectively, were found in the placebo and verum arms of the RCTs [47].

In order to distinguish the risk of RA patients resulting from chronic comorbidity or older age from the risk conveyed by treatment, comparison with other inflammatory rheumatic diseases with a lower background risk of infection is useful. No increased risk was found for anti-TNF agents in PsA [57], whereas the risk of serious infections in patients with AS was also found to be higher in those treated with TNF-α inhibitors. Compared with RA, these patients are younger, have less comorbidity and are usually not treated with GCs. Therefore their background risk of serious infections is clearly lower. Fouque-Aubert et al. [58], in their meta-analysis of trials with AS patients, observed a 1.9-fold RR of serious infection in the anti-TNF arms compared with the placebo arms.

Regarding meta-analyses of RCTs, methodological problems exist that we should be aware of when interpreting their safety results. Patients enrolled in trials are significantly different from those treated in daily care [59]. Only 25–33% of patients treated with cytokine-inhibiting treatment in daily care would fulfil trial inclusion and exclusion criteria [59]. Among the excluded patients are those with a higher susceptibility to serious infections: patients with a history of chronic infections, with severe comorbidities or low functional capacity.

Furthermore, meta-analyses of infrequent or rare events have to deal with the problem of zero events in one treatment arm. Division by zero is not calculable; this leads to incalculable ORs or RR estimates. Usually 0.5 events are added to zero in order to estimate RRs. However, adding 0.25 or 1.0 instead would change the results. Moreover, simulation results suggest that the frequently used Mantel–Haenszel method with a 0.5 zero-cell correction leads to biased results [60].

One important limitation is drawn from a finding described by Leombruno et al. [53]. The authors compared the serious infection risk in anti-TNF treatment arms with those of the placebo arms and found a decrease in the OR for serious infections in the verum arms of trials with longer duration. For RCTs with 26, 52 and 104 weeks duration they estimated ORs of 1.83, 1.48 and 0.98, respectively (Fig. 1).

Figure 1 illustrates that we have to consider changes in the infection risks over time not only in observational studies [31], but in RCTs as well. The reasons for these changes are similar in both types of studies: selective drop-out of high-risk patients and changes in clinical

Fɪɢ. 1 Regression of the logarithms of the ORs *vs* trial duration.
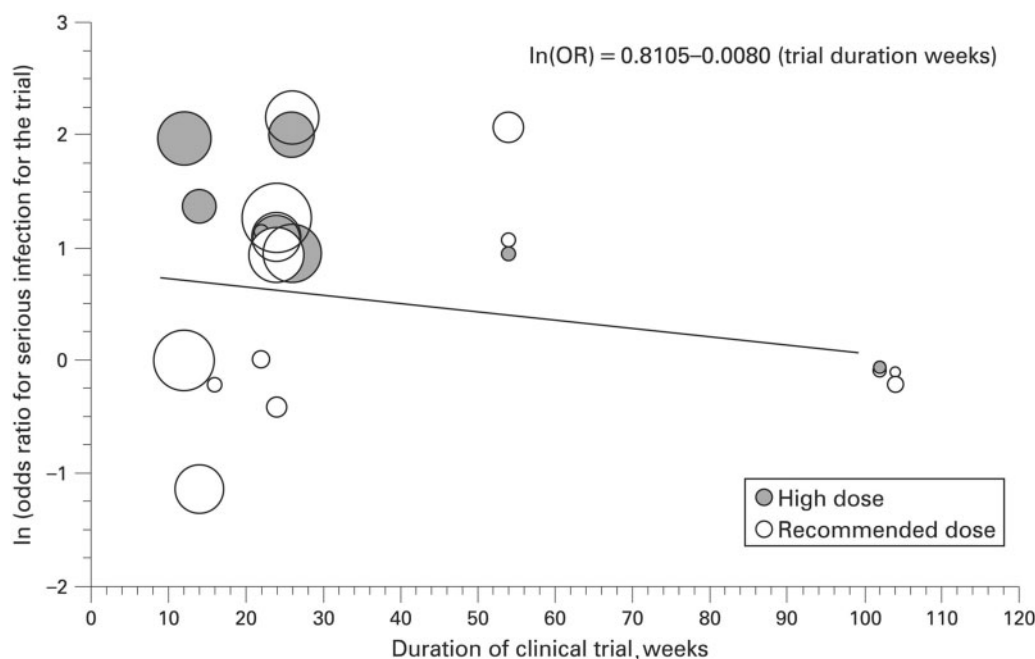
The size of the bubble is proportional in area to the trial's weight in the analysis. The shading of the circle is related to the dose used. β-Coefficient for duration is −0.00761/week, $P = 0.0512$. Reproduced from Leombruno *et al*. [53] with permission from BMJ Publishing Group Ltd.

status or co-medication. These time-varying risks have implications on the interpretation of study results. Considering this, the results of meta-analyses are an important source to estimate the risk of developing a serious adverse event (e.g. a serious infection) on the group level, in average patients and follow-up time, and presuming an average response to treatment. However, with these risk estimates physicians are not able to assess the risk of a treatment for an individual patient who may differ from the average patient, e.g. by age, comorbid conditions, co-medication with GCs, functional impairment or response to treatment.

Results of observational studies

Observational cohort studies on drug treatment observe unselected patients in daily care. They are able to include high numbers of patients and follow them for an undetermined period. Their ability to produce robust estimates on the safety of the drugs under observation and to detect possible safety signals of rare events is therefore superior even to very large RCTs. On the other hand, due to non-randomization, these studies are prone to confounding by indication. Even after careful adjustment, selection bias can never be entirely ruled out. Since observational studies follow the patients over very long time periods, they are also prone to attrition bias, i.e. selective loss to follow-up.

With the licensing of the first TNF-α inhibitors, the Societies for Rheumatology of various European countries took on responsibility for increased pharmaco-vigilance.

Independent drug registries were established in countries such as the UK, Sweden, Germany, Spain, Denmark and others, the majority with support from all pharmaceutical companies producing the agents [10]. Driven by the results from randomized trials and by considerations of the mode of immunological action of these substances, the major concerns pertained to the induction of malignancies, serious infections or autoimmune disease.

Initial results supported the assumption of an increased risk of serious infection from anti-TNF agents by showing a 2-fold increased risk compared with a DMARD control group after adjustment for baseline differences [61]. Subsequently, partly conflicting results were reported ranging from no [34, 62], to a moderately increased [32, 49, 63], to a 2-fold increased risk of serious infections [37]. A 4-fold increased risk was observed within the first 3 to 6 months of treatment with anti-TNF agents [37, 63]. A first explanation for the conflicting results was given by Askling *et al*. [64]. They found a decrease over time in the RR of hospitalization for infection in patients who remained on their first anti-TNF agent. The RR compared with conventional DMARD treatment decreased from 1.43 in the first to 1.15 in the second and 0.82 in the third year of treatment [64]. Further studies reproduced this time-dependent decrease in risk. A common conclusion was that the increased risk of infection was confined to the first 3–6 months of treatment. But the question remained: why?

Methodological considerations included, among others, confounding by indication, which means that patients

treated with cytokine inhibitors in daily care are in general more severely ill than patients receiving conventional DMARDs. This problem was taken into account in most of the studies. Patient characteristics assessed at the start of treatment were used to estimate the likelihood of a patient receiving anti-TNF treatment. This likelihood or propensity score was then used to stratify patients into groups with a similar propensity score. Comparisons between anti-TNF- and DMARD-exposed patients were made within the propensity score strata, i.e. between patients with rather similar risk profiles at baseline.

This approach is able to adjust for differences in patient characteristics at the start of treatment, but has the disadvantage of being static. Changes in risk profiles over time are not considered. Severely affected patients are treated with more potent immunosuppressive drugs to reach the clinical status that other patients have already achieved with less immunosuppressive treatments. Not taking these changes into account may lead to false conclusions.

For example, patients with a history of serious infection have a higher risk of developing further serious infections [31, 48, 65]. Withdrawal from anti-TNF treatment or dropping out of a study because of serious infections therefore leads to the depletion of patients susceptible to infections and to patients with lower risk remaining in the cohort. Since these drop-out processes do not happen at random, they can seriously bias the results [31]. In light of this, the results from Grijalva et al. [66], who reported no increased risk under TNF inhibitors based upon claims data, have to be treated with caution since their drop-out rates exceeded 50% in one group within the first 4 months of follow-up. In addition, fluctuating GC dosages or changes in functional capacity, both of which have a significant impact on the development of infections, have to be considered. Therefore adjustment for the GC dose only at baseline is of limited value.

Tuberculosis and opportunistic infections

Soon after licensing, TNF inhibitors were already described as associated with an increased risk of severe tuberculosis [67, 68]. The cases tended to be unusually severe and to present with extra-pulmonary disease [67]. In the Spanish Society for Rheumatology biologics register, a more than 20-fold increased risk was found for patients treated with TNF inhibitors compared with the general population, and a 7-fold risk compared with an unexposed RA cohort. However, after implementing screening guidelines, this risk decreased to a 4-fold risk compared with the general population and no increased risk compared with other RA patients [69, 70]. The higher risk of reactivation of tuberculosis with TNF inhibitors, in particular the monoclonal antibodies, was confirmed in the Swedish register in 2005 [71] and the British register in 2010 [72]. A few cases of tuberculosis have been reported under abatacept and tocilizumab, and screening

before initiation of therapy is recommended for these substances as well [73].

The British Biologics Register compared the risk of tuberculosis in 10 712 patients treated with infliximab, adalimumab or etanercept. Forty cases of tuberculosis were observed in 34 025 patient-years of follow-up. The risk for etanercept was lowest, with 0.39/1000 patient-years, and higher for the monoclonal antibodies (3.1 times higher for infliximab and 4.2 times higher for adalimumab compared with etanercept) [72].

In the first years after licensing of TNF inhibitors, various case reports and results from spontaneous reporting systems suggested an increased risk of opportunistic infections under TNF inhibition. These reports included infections with *Toxoplasma*, *Listeria*, *Histoplasma*, *Leishmania*, coccidioidomycosis, *Legionella*, candidiasis, *Pneumocystis jirovecii* and aspergillosis (for details see Martin-Mola and Balsa [73] and Strangfeld and Listing [74]). However, these reports mainly originated from endemic areas or were related to severely immuno-compromised patients. They indicate that, although not common, risk might be increased in patients receiving cytokine-inhibiting treatment. Measures to minimize the risk follow the general guidelines for immunocompromised persons: avoid non-pasteurized food, observe travel warnings, vaccinate against common infections.

Infection risk in individual patients

As discussed above, estimates of the risk of serious infections are usually based on averages over patients and follow-up time. They allow a rough estimation of the risk of a treatment in general but are inadequate to assess the risk of individual patients at a certain point in time, e.g. when treatment decisions have to be made.

A first attempt to overcome this limitation and enable the rheumatologist to assess the risk of patients individually based on their current status was made by the German biologics register RABBIT (Rheumatoid Arthritis Observation of Biologic Therapy). In this analysis, time-varying changes in functional status, treatment with TNF inhibitors and GC dosages were considered [31]. Thus patients were considered as being at risk of high dosages of GC only for the time interval they were exposed. If the dosage could be tapered down due to lower disease activity, the actual lower GC dose was taken into account. The analysis resulted in estimates for relative and absolute risks. Compared with treatment with synthetic DMARDs, a nearly 2-fold-increased risk (RR = 1.8; 95% CI 1.2, 2.7) of developing serious infections was found for patients treated with TNF inhibitors. Two- (RR = 2.1; 95% CI 1.4, 3.2) to more than 4-fold (RR = 4.7; 95% CI 2.4, 9.4) increased risks were observed for patients receiving 7.5–14 mg/day and ⩾15 mg/day GCs, respectively. Of note, these risks were constant over the time the patients were exposed to these drugs and allowed the estimation of absolute risks (incidence rates), as shown in Table 1.

For example, an RA patient aged 65 with chronic obstructive pulmonary disease (COPD) has two risk

TABLE 1 Estimated incidence rates of serious infections per 100 patient-years with 95% CIs in parentheses

GCs	Risk factors[a] (95% CI)			
	None	One[a]	Two[a]	Three[b]
DMARDs				
0 to <7.5 mg/day	0.9 (0.6, 1.4)	1.5 (1.0, 2.2)	2.5 (1.5, 4.2)	5.3 (2.5, 11.4)
7.5–14 mg/day	2.0 (1.2, 3.2)	3.2 (1.9, 5.3)	5.4 (3.1, 9.3)	11.4 (5.8, 22.6)
⩾15 mg/day	4.4 (2.1, 9.2)	7.1 (3.3, 15.4)	12.0 (5.8, 24.8)	25.4 (10.8, 59.4)
TNF inhibitors				
0 to <7.5 mg/day	1.7 (1.2, 2.3)	2.7 (2.0, 3.7)	4.6 (3.0, 7.1)	9.7 (4.5, 20.8)
7.5–14 mg/day	3.6 (2.3, 5.6)	5.8 (3.6, 9.4)	9.8 (5.8, 16.3)	20.7 (10.0, 42.8)
⩾15 mg/day	8.0 (3.9, 16.4)	12.9 (6.0, 27.7)	21.7 (10.7, 44.3)	45.9 (18.9, 111.7)

[a]One or two of the following risk factors: age >60 years, chronic lung disease, chronic renal disease or high number of treatment failures. Considering a history of serious infections as a risk factor would have led to ~30% higher incidence rates. [b]Two risk factors (see above) plus history of serious infections. Adapted from Strangfeld *et al.* [31] with permission from BMJ Publishing Group Ltd.

factors (older age and COPD) in addition to RA. Assuming this patient is treated with MTX and 7.5 mg/day GCs, in 100 patients with such a risk profile, 5.4 serious infections are expected to be observed per year. In the case that the treatment of this patient is insufficient and the GC dose has to be increased to 15 mg/day, the expected rate would be 12 serious infections/100 patient-years (Table 1). Switching to a TNF inhibitor instead would increase the risk to 10 infections/100 patient-years, but if the new treatment is effective and the GC dose can be tapered down to <7.5 mg/day, the expected rate is only 4.6/100 patient-years. This example describes the impact of different treatment options for individual patients, as well as explaining how anti-TNF agents may influence the infection risk at the level of the individual patient. The RABBIT risk score was recently validated on a new patient cohort of 1327 RA patients treated with TNF-α inhibitors and of 1276 patients treated with synthetic DMARDs. A high agreement between expected and observed infections was found [75]. Crowson *et al.* [48] developed a similar risk score based on data of 609 patients of the Rochester cohort, which does not, however, include treatment with biologic agents.

Summary

Patients with RA have elevated susceptibility to serious infections due to features of the disease itself, comorbidity and immunosuppressive treatment. GCs increase the risk by a factor of two to four in a dose-dependent manner. TNF-α inhibitors increase the serious infection risk up to 2-fold. Meta-analyses suggest a similar increase for non-anti TNF biologics.

Biologics have the potential to outweigh their risk when higher GC doses can be tapered down. However, if patients need higher dosages of GCs despite treatment with biologic agents, their risk of infection is substantial. This combination has to be used carefully and, if possible, avoided in patients with additional risk factors such as older age or comorbid conditions.

Rheumatology key messages

- Active RA is associated with an increased risk of serious infection.
- GCs and biologic agents increase the susceptibility for serious infections in patients with RA.
- The evidence from observational studies allows estimation of infection risks in individual RA patients.

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