Serious Infections in Rheumatoid Arthritis and Strategies for their Prevention - A Review and Discussion of Implications for Clinical Practice

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List of Abbreviations

BSRBR: the British Society for Rheumatology Biologics Register; RABBIT: German Registry Review (GDR); DREAM: Dutch Rheumatoid Arthritis Monitoring Registry (Netherlands) GISEA: Registry (Italy, Italian Group for the Study of Early Arthritis), ARAD: Australian Rheumatology Association Database; sDMARDs and bDMARDs: synthetic and biological disease-modifying antirheumatic drug, respectively.

Introduction

Rheumatoid Arthritis (RA) is a chronic, systemic autoimmune disorder. It affects over 1% of the world population and confers significant economic burdens, not only on the individual, but also society as a whole. The rheumatoid patient is exposed to many complications including infections, cardiovascular disease and malignancy.

Among these, serious infection (SI) (infection that is life-threatening or fatal) requires hospitalization or intravenous antibiotics or results in severe disability) is of special importance, because of the immediate risk of mortality, ongoing morbidity and because of the health economic implications. Serious infections are still the number one cause of death in RA globally.

The most prevalent infections in RA include bronchopulmonary, urogenital, soft tissue and skin, bone/joint sepsis and gastrointestinal infections [1]. Infections in the lung and urogenital system or generalized sepsis in a patient with RA is common.

Keywords: Infections, Arthritis, Serious infections, Risk factors

Abstract

Introduction: Serious infections (SIs) in rheumatoid arthritis (RA) are common and may be life-threatening or fatal. The goal of this review was to assess the spectrum of SIs in RA; review potential causes for these SIs and to formulate strategies for prevention.

Methods: We performed a systematic review that included multiple databases viz. PubMed, Medline, Scopus, and Google Scholar. Search terms used were ‘Rheumatoid Arthritis AND infection’. Searches were limited to the title of articles, human subjects and non-juvenile arthritis and to those articles published in English.

Results: In total, 3,324 articles, identified through PubMed, Medline, Scopus and Google Scholar repository were found. After removing duplicates, 825 articles remained for further screening from which 141 articles were selected. These were further assessed and 110 were then excluded because 31 articles were case reports, 35 focused on young subjects (<16 years) and 44 studies focused on non-serious infection. Overall, only 31 studies met our selection criteria.

Conclusion: SIs are far more common in RA than in the general population. Corticosteroids are associated with an appreciable increase in SI risk. Most commonly used and currently favored synthetic DMARDs confer a small or no risk, biologic DMARDs confer moderate risk in the first year of therapy and then a diminishing risk thereafter, and higher dose biologic or combination biologic therapy should be avoided since the SI risk is unacceptably high. Undetectable Mannose Binding Lectin (MBL) is a major risk factor for SI in RA, comparable to Prednisolone.

Keywords: Infections, Arthritis, Serious infections, Risk factors

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and may be fatal, with incident frequencies up to ten times that in the general population [2,3]. Less commonly, infection in RA may affect the central nervous system (CNS), the cardiovascular system or the lymphatic system [4].

It is clear that in RA, there is a marked increase in rates of SI from less than 1 per 100PYs in the normal population to around 5 per 100PYs in RA overall [5]. Bronchopulmonary, urogenital and skin infections are the most common SIs. The main pathogens are *S. pneumoniae*, *S. aureus*, gram-negative bacilli and anaerobes [6]. Some studies have investigated diverse risk factors, such as RA disease pathophysiology, RA medication and immunodeficiency including MBL deficiency as potential causes for this higher incidence rate [2,7-15] A failure to appreciate this *de novo* increase in frequency of SIs in RA can give rise to a perception of more frequent SIs in sDMARD and bDMARD treated RA.

In this review, we have searched the literature in order to determine and analyze (i) the extent to which RA patients are predisposed/susceptible to developing SIs (ii) identify potential risk factors associated with SIs in RA patients (iii) whether the rate of SIs is higher in patients who are on medications, such as anti-TNF-α, and DMARDs. The goal was to identify, categorize and evaluate the main causes of SIs in RA. In addition, methods and possible strategies to minimize or prevent infection in RA and in turn reduce the rate of hospitalization and out of hospital treatments will be discussed.

**Methods**

**Search strategy and selection criteria**

We performed a systematic review that included multiple databases viz. PubMed, Medline, Scopus, and Google Scholar. Search terms used were 'Rheumatoid Arthritis AND infection'. Searches were limited to the title of articles, human subjects and non-juvenile arthritis and to those articles published in English. The search timeframe was 1996-2015. Articles were only included in this review if they investigated or discussed 'infection in Rheumatoid arthritis' specifically focusing on SI in patients over 16 years of age. Eleven cohorts, four reviews, one cross-sectional study, one observational prospective study, five case-control studies, five randomized controlled trials (RCT), three systematic reviews and two meta-analyses were included. Even though diverse methodologies and a relatively long time-frame mitigating against embracement of the modern biologic era were used, the advantages of inclusivity were deemed to outweigh the inconsistencies in methodology. A PRISMA chart has been constructed to show the systematic selection of the articles (Tables 1 and 2).

**Results**

**Study selection**

In total, 3,324 articles identified through PubMed, Medline, Scopus and Google Scholar repository were found. After

<table>
<thead>
<tr>
<th>Medication</th>
<th>Bacteria</th>
<th>Fungal/ Protozoan</th>
<th>Viral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids Cyclophosphamide and alkylating agents Azathioprine</td>
<td>Gram-positive: Staphylococcus aureus</td>
<td>Candida albicans</td>
<td>- Human herpes virus-6</td>
</tr>
<tr>
<td></td>
<td>Gram-negative: Escherichia coli</td>
<td>- Coccidioides immitis</td>
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<td></td>
<td>Klebsiella pneumonae</td>
<td>- Cryptococcus neoformans</td>
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<td></td>
<td>Pseudomonas aeruginosa</td>
<td>- Pneumocystis carinii</td>
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<tr>
<td></td>
<td>Other Enterobacteriaceae</td>
<td>- Strongyloides stercoralis</td>
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<tr>
<td></td>
<td>Mycobacterium spp</td>
<td>- Histoplasma capsulatum</td>
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<td></td>
<td>Listeria monocytogenes</td>
<td>- Toxoplasma gondii</td>
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<td></td>
<td>Salmonella spp</td>
<td>- Adenovirus</td>
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<td></td>
<td>Nocardia spp</td>
<td>- Varicella zoster virus</td>
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<td></td>
<td></td>
<td>- Epstein-Barr virus</td>
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</table>

Table 1: Relationship between medications and infections in RA leading to defective cell-mediated immunity.

<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>Rate of SIs per 100PYs (synthetic DMARD)</th>
<th>Rate of SIs per 100PYs (biologic DMARD)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galloway J B, et al. (2011)</td>
<td>BSRBR Registry Review (UK)</td>
<td>3.20 (sDMARD controls)</td>
<td>4.20 (all Bx DMARDs)</td>
<td>[63]</td>
</tr>
<tr>
<td>Doran, et al. (2002)</td>
<td>RA vs Population Controls</td>
<td>19.23 per 100 PYs*</td>
<td>NA</td>
<td>[30]</td>
</tr>
<tr>
<td>Listing, et al. (2005)</td>
<td>German RABBIT Registry Review (GDR)</td>
<td>2.28 (sDMARD controls)</td>
<td>6.15 (INX) and 6.42(ETA)</td>
<td>[17]</td>
</tr>
<tr>
<td>Lacaille, et al. (2008)</td>
<td>Large RA cohort (n=27,710)</td>
<td>4.5 -5.5 per 100PYs</td>
<td>NA</td>
<td>[27]</td>
</tr>
<tr>
<td>Greenberg, et al. (2010)</td>
<td>MTX vs controls (n=7,971)</td>
<td>3.1 – 3.2 per 100 PYs#</td>
<td>NA</td>
<td>[24]</td>
</tr>
<tr>
<td>Askling J, et al. (2006)</td>
<td>Swedish Biologics Register</td>
<td>4.5 (INX, ETA and ADA)</td>
<td></td>
<td>[39]</td>
</tr>
<tr>
<td>Atzeni, et al. (2012)</td>
<td>GISEA Registry (Italy)</td>
<td>NA</td>
<td>3.18 (for INX, ADA and ETA)</td>
<td>[48]</td>
</tr>
<tr>
<td>van Dartel SAA, et al. (2012)</td>
<td>DREAM Registry (Netherlands)</td>
<td>NA</td>
<td>2.91 (over 5 years)</td>
<td>[14]</td>
</tr>
</tbody>
</table>

Table 2: Summary of studies showing the rate of SIs in patients treated with synthetic and biologic DMARDs

*PYs: Patients years - For the period 1955 – 1994, rates may have declined over time
#Mean follow-up (period of observation) was 1.4 years
^ ETA, INX and ADA
removing duplicates, 825 articles remained, from which upon further screening, 684 articles were culled due to one or more of the following: (i) population size was very small or the studies were not within the designated time frame; namely 1996-2015 (ii) heterogeneous populations, which made it difficult to identify infections pertaining explicitly to RA and (iii) the language in which the articles were published was not English. The full texts of the remaining 141 articles were assessed and 110 were then excluded because, 31 articles were case reports, 35 focused on young subjects (<16 years) and 44 studies focused on non-serious infections pertaining explicitly to RA and (iii) the language in which the articles were published was not English. The full texts of the remaining 141 articles were assessed and 110 were then excluded because, 31 articles were case reports, 35 focused on young subjects (<16 years) and 44 studies focused on non-serious infection. Overall, only 31 studies met selection criteria (Figure 1).

**Pathogen categories**

Nolla, et al. (2000) reported that among RA patients, during 1990-1998, the most prevalent bacterial infections were *Staphylococcus aureus* and *Streptococcus pneumoniae* [16]. Both are gram-positive cocci. They also showed that skin infection was the principal source of infective disease in RA patients and *S. aureus* was among the most important pathogens for septic arthritis. *S. pneumoniae* was also a relevant pathogen in septic arthritis in RA patients, but it was less frequent. The majority of cases of septic arthritis in RA were mono-articular with involvement of the knee, elbow and wrist most often reported (Tables 1 and 3) [6].

**Risk factor categories**

Many studies have shown a greater than 2-fold increased risk of SI in RA patients [1,2,7-20]. There are several contributing factors involved. Briefly these include:

- The pathobiology of the disease itself;
- Chronic comorbid conditions: such as diabetes mellitus, heart failure, lung or kidney disease, bronchiectasis and alcoholism;
- Age: Elderly-onset RA patients are most at risk;
- Drug dosage, duration of treatment, and side effects: it has been shown that some drugs at high dosage and prolonged treatment therewith confer significant risk, especially in older patients with RA;
- The immunosuppressive nature of at least some of the drugs used to treat RA: These include a range of medications such as corticosteroids, synthetic DMARDs, and biologic DMARDs;
- Genetic factors: These include Mannose Binding Lectin (MBL) deficiency, which has recently been shown to contribute significantly to serious infections in RA and which is the commonest form of innate immune deficiency. In addition, hypogammaglobulinaemia (common variable immunodeficiency or CVID and selective IgA deficiency or SlgAD), which are a good deal less common, may nevertheless, occasionally contribute to SIs. Roberts, et al. (2015) have reported immunoglobulin deficiency after rituximab for lymphoma and rheumatoid arthritis [21,22].
- Lifestyle factors: such as poor diet, reduced physical activity, smoking, and alcohol consumption.

**The impact of medications (non-biologics)**

A summary of studies showing the rate of SIs in patients treated with synthetic and biologic DMARDs is shown in Table 3. Galloway, et al. (2011) showed the SI incidence rates to be 42/1000 and 32/1000 patient-years for anti-TNF and sDMARDs respectively. And the risk did not differ significantly between the three agents; adalimumab, etanercept and infliximab. The risk was highest during the first 6 months of therapy [23].

Greenberg et al. showed that a major risk factor for infection is the immunosuppressive therapy used. They also showed that newer therapies for RA may lead to increased rates of infection by pathogens such as *Mycobacterium tuberculosis* [24]. In another study to examine the association of methotrexate (MTX) and tumour necrosis factor (TNF) antagonists with the risk of infectious, Greenberg et al. showed that MTX, TNF antagonists...
and prednisone at doses >10 mg daily were associated with increased risks of infections overall. Low-dose prednisone and TNF antagonists (but not MTX) increased the risk of opportunistic infections [24]. Van Daltel, et al. (2013) showed the incidence rates for a first serious infection in patients with RA per 100 patient-years were 2.61, 3.86 and 1.66, for adalimumab, infliximab and etanercept respectively [14]. The impact of other medications is discussed below.

Corticosteroids: Corticosteroid (CS) use is a major contributor to SIs in RA. The effects are dose- and duration-dependent [25]. Both high dosage and the duration of CS treatment confer significant risk, especially in older patients with RA. The infection risk has been clearly shown to be dose dependent, but whether there is a minimum safe dose with respect to serious infection risk is unclear. Of considerable concern, a patient who has taken at least 5 mg of prednisolone daily for 3 months has a 30% chance of hospitalization due to infection [26]. Therefore, in the treatment of RA, in order to minimize the risk of an SI, the lowest possible dose of CS for the shortest possible duration should be prescribed [25]. Increasingly, with the advent of more effective synthetic and biologic DMARDs, the scope to progressively taper and switch from CS to DMARDs alone has increased.

Listing, et al. showed that there is evidence that glucocorticoids (GCs) increase the risk of serious infections up to 4-fold in a dose-dependent manner. In addition, anti-TNF-α inhibitors increase the serious infection risk up to 2-fold. The risk of infection is substantial if patients need higher dosages of GCs in addition to treatment with anti-TNF-α therapy. It was recommended that such combination therapies should be avoided, if possible, especially in patients with additional risk factors such as older age or comorbid conditions [20].

Synthetic DMARDs: Whether synthetic DMARDs at recommended doses contribute to infections in RA is uncertain and still a matter of conjecture. Laclaire, et al. (2008) conducted a retrospective, longitudinal study of a population-based RA cohort in British Columbia, Canada (from January 1996 to March 2003). In this study, a total of 27,710 RA patients provided 162,710 person-years of follow-up. The authors showed that 92% of patients had at least one type of mild infection and 18% had a SI. Corticosteroids were shown to be unequivocally implicated in SIs with an adjusted rate ratio of 1.9 (CI 1.75-2.05) [27]. Importantly, these investigators showed that use of DMARDs without corticosteroids was not associated with an increased risk for SI [adjusted rate ratio of 0.92 (CI 0.85-1.00)]. They concluded that unlike corticosteroids, synthetic DMARDs in general do not elevate the risk of serious infection in RA. It is however worth noting that, in their study, the SI rate for RA patients receiving cyclophosphamide (CYC) was 19.8 to 39.4 per 100 patient years of exposure, which is well above the rate seen for SIs in RA overall (~ 4.4 to 5.5 per 100 Pys in their study), suggesting that some immunosuppressive DMARDs might still be an exception to the rule. CYC of course is now rarely used as a DMARD in some immunosuppressive DMARDs might still be an exception overall (~ 4.4 to 5.5 per 100 Pys in their study), suggesting that with methotrexate for treatment of severe RA, CYC can increase the rate of urinary tract infection (UTI) [7,28].

Methotrexate (MTX, Methoblastin) related infections are varied and appear to be dose dependent. Because MTX is commonly used in combination with other drugs, it is often difficult to assess the contribution of MTX alone. There have been several studies which have investigated MTX and its role in the development of infection. For example, in a randomized controlled trial (RCT), incorporating 571 RA patients who were treated with a mean MTX dosage of 10.8 mg/week, without concomitant biological DMARDs, Sakai et al. (2011) showed that MTX did not confer an increased risk for serious infections in RA patients [15]. However, there were limitations to this study, not least the lower mean dosage of MTX than that commonly used in the United States, Australia and Europe. Boerboom and et al. (1995) in a 6-year open prospective study and in a 12-month randomized double blind trial comparing MTX with AZA, showed that the infection rate during MTX treatment was higher in severe RA than in moderate RA. Once again this highlights the likely contribution of inherent disease activity to SI risk [29].

Doran, et al. (2010) who followed a total of 7,971 patients showed that the rate of infection per 100 person-years was increased among MTX users. They expanded their studies to TNF antagonists and prednisolone and concluded that both MTX and Prednisolone, at doses more than 10 mg daily, were associated with increased risks for infections overall [24]. Bernatsky, et al. (2007) in a cohort of 23,733 RA patients, showed that methotrexate increases the rate of pneumonia (RR: 1.16, 95% CI: 1.02–1.33) [7] (Table 2).
is increased risk of diverse infections. These include (i) bacterial infections such as Gram-positive and Gram-negative bacteria, *Mycobacterium tuberculosis*, atypical mycobacterial infection, *Listeriosis monocytogenes*, (ii) viral infections e.g. cytomegalovirus (CMV), and (iii) fungal infections e.g. *Pneumocystis jirovectii*, aspergillosis, histoplasmosis, coccidioidomycosis and cryptococcal infections [34,35].

The evidence for re-activation of *Mycobacterium tuberculosis* infection in RA patients has been discussed in at least two different studies [36]. All TNF inhibitors have a propensity to re-activate tuberculosis. Infliximab appears to confer greater risk than Etanercept [31,34]. There is also a significantly increased rate for Hepatitis B virus reactivation, especially when immunosuppression is diminished or withdrawn. Therefore, a combination of treatments with hepatitis B (HB) antiviral agents in conjunction with TNF inhibitors is suggested in patients with evidence of previous HB infection [35]. In addition, there is a known, albeit small, increase in risk for herpes zoster and a very small risk for leukoencephalopathy (PML) in TNF inhibitor recipients [36,37]. Historically, the greatest risk for PML has been associated with use of Natalizumab in multiple sclerosis, but the risk for TNF blockers and Rituximab in RA is not negligible and will require further study to accurately quantify [31,38] and predict susceptibility. A meta-analysis in 2006 revealed that anti-TNF treatment can also increase the risk of serious pyogenic infections [8]. The German Biologics Registry investigators found the risk of serious pyogenic infection to be two-fold [8,10,17]. In contrast to the above studies, the BSRBR and the Swedish Arthritis Treatment group have reported that a non-significant relative risk ratio exists for severe infections in patients treated with TNF inhibitors [10,39]. These differences may be explained by the longevity of the studies. SIs appear to be much more frequent within the first year of usage / observation. Thus, long term follow-up studies may report lower rates of SI compared to short-term studies.

It is worth noting that van Dartel, et al. (2012) found that Adalimumab and Infliximab conferred higher; albeit similar risks for serious infection in RA patients, whereas Etanercept conferred lower risk [14]. In addition, Trung, et al. (2013) in their studies provided a table to categorize the risk of infection with different anti-synovitis medications. In that study, it is reported that Etanercept, Infliximab and Golimumab were associated with the highest rates of serious infection. It was shown that Etanercept, Adalimumab, Abatacept and Tocilizumab were associated with opportunistic infections and tuberculosis (TB) [40]. In a systematic review by Greenberg et al. (2002), it was demonstrated that some of the anti-TNF medicines increased the rates of opportunistic infections while traditional immunosuppressants such as corticosteroids and synthetic DMARDs were major risk factors for serious infection in RA (Table 2) [2]. Moreover, Dixon et al. (2006) in an observational study of a large cohort of RA patients (n=7664) enrolled in the BSRBR, emphasized the important role that TNF has in host defense in the skin and soft tissue [10]. In their study, patients who were treated with anti-TNF-α agents, as compared to synthetic DMARDs, developed more serious skin and soft tissue infections. However, importantly, they found that the overall risk of serious infection for anti-TNF medicines compared to synthetic DMARDs was the same in both groups [10].

**Abatacept (ABT), Rituximab, Anakinra, Tofacitinib and Tocilizumab:** ABT safety has been evaluated in several long-term extension (LTE) studies (duration usually 2-3 years). Within this timeframe, in respect to SIs, ABT performs well with SI rates of 1.6 to 3.6 per 100 PYs of treatment in age unstratified RA recipients [41,42]. Given that up to 60% of these patients were also taking corticosteroids in doses not always clearly defined, the rates are low for the most part and somewhat lower than for most other biologic agents (Table 3). The elderly are more vulnerable as is true in respect to SIs in general and especially after there has been an antecedent hospitalization for infection. For ABT, rates of 26.5 per 100 PYs apply for ABT and 36.1 for ETA [42,43]. Lahaye, et al. found that SI rates in Abatacept recipients rose progressively from 1.73 per 100 PYs in persons under 50 to 4.65 in persons 50-64, 5.90 in persons 65-74 and 10.38 per 100 PYs in persons equal to or greater than 75 years of age [43]. Thus, whilst relatively safe in the young and up to extended middle age, the SI rates rise concerningly for ABT in those over 65 years of age and especially when there has been an antecedent hospitalization for an infection (Table 3).

For Rituximab, Tocilizumab and Tofacitinib, the rates of SI are comparable to those reported for all TNF inhibitors. However, it should be noted that the cumulative exposure for most of these agents, like the TNF inhibitors is limited and mostly does not exceed 2 years. Furthermore, not enough additional data is available to evaluate associated SI risk factors in these cohorts. For example, a breakdown for age, corticosteroid dosage and important comorbidities such as diabetes, neutropaenia and lymphopaenia is not available sufficiently often to allow these parameters to be taken fully into account in respect to their independent or additive effect on SI risk.

In the case of Infliximab (INX) and tocilizumab (TCZ) there is some data, which suggests that SIs are dose dependent with higher rates seen with higher doses [44]. This has already been referred to in respect to INX. For TCZ, SI rates of 3.4 per 100 patient years (100PYs) were observed for comparators, 3.5 per 100 PYs for TCZ 4 mg/Kg and 4.9 per 100 PYs for TCZ 8 mg/Kg [45]. In contrast, for Rituximab (RITUX), the SI rates for 500 mg x 2 versus 10.00 mg x2 at 24-week intervals were similar at 2.62 and 1.96 SIs per 100PYs [46].

Salliot, et al. [47] investigated the risk of SIs during treatment of RA with rituximab, abatacept and anakinra. SI frequencies were investigated using meta-analyses of randomized placebo-controlled trials. It is important to remember that this approach inevitably is short term due to the design of the trials. Moreover, sicker patients are often excluded. Nevertheless, no significant increase in the risk for SIs attributable to these biologies was observed. The authors concluded that, based on these randomised placebo-controlled trials, rituximab, abatacept and anakinra have a relatively good safety profile for SIs. However, an increased risk for SIs was observed for high doses of anakinra (>100 mg per day) in patients with comorbidities.

**Risks associated with combination therapies:** It is now common practice to combine synthetic DMARDs with biologic DMARDs, since efficacy is greater. Some studies have shown that synthetic DMARDs in combination with anti-TNF-α increase the rate of SIs. For example, Atzeni, et al. (2012) in a case control study examined 2,769 patients with long term RA [48]. Treatment with corticosteroids and other synthetic DMARDs in combination
with various anti-TNF agents, viz. Infliximab (INX), Adalimumab (ADA) and Etanercept (ETN), was investigated. The authors found that the risk of SI was significantly different across these medication groups (p<0.0001). In these patients, the following factors were identified as significant infection predictors: (i) The concomitant use of corticosteroids (p=0.046 with hazard ratio (HR) of 1.849) (ii) concomitant DMARD treatment during anti-TNF therapy (p=0.004 with HR of 2.178) (iii) advanced age at the start of anti-TNF treatment (p=0.001 with HR of 1.03) and (iv) the use of INX or ADA rather than ETN (p<0.0001 with HR 4.291 for INX vs ETA and p=0.023 with HR 1.942 for ADA vs ETA). In this study the authors also found that treatment with anti-TNF was associated with a small, but statistically significant risk of SI (HR of 1.03 and P < 0.0001). In Atzeni et al’s study, disease duration and the disease severity score were not found to be predictive of serious infection [48].

In a systematic study by Campbell, et al. (2011), the effect of tocilizumab (TCZ), in combination with MTX, in patients with RA was investigated [49]. The researchers concluded that this combination treatment for RA is associated with a small, but significantly increased risk of adverse effects and infections. Their meta-analysis revealed that tocilizumab 8 mg/kg compared with controls increased the risk of infection. This risk is comparable with other biologic agents, although the risk of serious infection may be less than that for TNF antagonists.

Perhaps more so than any other biologic agent, the capacity of IL-6 antagonists to markedly reduce CRP further compounds the difficulty to recognize serious infection, since great reliance is usually placed on the CRP concentration when determining the probability of an SI in an unwell rheumatoid patient. Such delays may adversely affect patient outcomes.

**Tuberculosis (TB) and non-tuberculous mycobacterial (NTM) infections**

In a recent meta-analysis conducted by Winthrop, et al. (2015), both TB and NTM infections were shown to be increased in patients with RA who have been treated with a range of biologics [36,50]. These include Infliximab, Etanercept and Adalimumab, which target TNF-α, as well as Rituximab, which targets CD20 receptors on the surface of B cells. All these agents have been shown to re-activate TB and predispose to NTM infections, albeit at different rates. Infliximab was implicated in TB and NTM infections (11 and 7 cases respectively). In contrast, in this meta-analysis Abatacept was not shown to predispose to TB or NTM infections. It remains important to carefully screen for latent TB, both clinically and otherwise (Mantoux skin testing, Quantiferon GOLD testing) and where necessary, to treat these conditions appropriately before initiating bDMARD’s in RA.

**Serological and other laboratory parameters that influence SI risk**

Diverse cellular and serological abnormalities are known to increase susceptibility to infection. These include neutropaenia, especially in the context of Felty’s syndrome, where high disease activity is often a factor as well, lymphopaenia, immunoglobulin deficiencies (innate and acquired) and terminal complement deficiencies, although the frequency of Ig and terminal complement deficiency is low or very low respectively. Mannose binding lectin deficiency is far more common with frequencies in the order of 5-8% in the population in general and 8 - 15% in rheumatoid populations.

**MBL and other immune deficiencies**

Mannose Binding Lectin (MBL) deficiency is implicated in a variety of infections in neonates and children, but less so in otherwise healthy adults [11,51-53] MBL is a component of the innate immune system. It is a carbohydrate binding protein produced by the liver and is involved in innate immunity [54]. Structurally, this molecule comes in trimer and tetramer forms and binds to the glycan on the pathogen’s cell surface mannose receptor. Generally, *immune-compromised* patients and patients with chronic diseases or impaired adaptive immune systems including those with MBL deficiency have increased risks of serious infection [11,55-57] MBL has also been shown to have roles in manifestations of RA disease and the development of other complications of RA, such as cardiovascualr disease [58].

In a recently reported study of risk factors for SIs in RA, both undetectable MBL and CS use (prednisolone at doses of 5 mg per day or more) were shown to confer a 4-5 fold increased risk for SIs [53]. This takes on greater importance when it is remembered that up to 15% of RA patients have undetectable MBL and that rates of CS use in RA, although they vary a great deal from centre to centre are still high despite the availability of more efficacious DMARDs (up to 70%) [53]. In fact, apart from severe neutropaenia, such as in Felty’s syndrome for example, no other laboratory marker appears to confer greater SI risk then undetectable MBL. Common variable immunodeficiency (CVID) is estimated to affect up to 1 in 25,000 individuals and can be associated with auto-immune diseases including RA [59-61]. The exact risk associated with CVID or its various disease expressions such as panhypogammaglobulinaemia, selectively reduced immunoglobulins (e.g. IgA deficiency) and IgG subset deficiency in RA is unknown, but given that these deficiencies are much less frequent than undetectable MBL, they are likely to be relatively less important clinically.

Selective IgA deficiency or S IgAD, which is the most common of these immunoglobulin deficiencies, occurs in less than 1 in 100 persons of Arabic descent and in less than 1 in 800 Caucasians in the UK. Although increased rates of severe respiratory tract infections are observed in IgAD persons, compared to unaffected controls (3-fold increased risk), life-threatening infections were not recorded in this group [62] Elsewhere, risk factors predisposing to the development of hypogammaglobulinaemia and infections post-rituximab treatment have been reported [63]. Terminal complement components C5 - C9, otherwise referred to as the membrane attack complex also predispose to recurrent infection, especially with encapsulated organisms, such as Neisseria, but do not appear to associate strongly with auto-immune diseases and are relatively rare in Caucasians, although not in Afro-Americans and probably not in native Africans.

**Implications for Clinical Practice**

The treating clinician needs to consider the following when choosing therapeutic agents for patients with RA who are at risk for SIs:

**Age**
SIs are substantially increased in persons of advanced age -for example in a large USA Medicare beneficiaries cohort, the SI rate in those over 65 was 14.2 per 100PYs compared to 4.8 in those less than 65 years of age [43]. A recently reported study by one of the authors indicates that the risk of an SI increases by 19% for every 5 year increase in age and by 41% for every 10 year increase in age [53]. The prescribing clinician should take into account, the differing relative risks for SIs when prescribing DMARDs for the old and the very old rheumatoid patient.

Corticosteroid (CS) Use and Dosage

In RA patients, the SI risk is appreciably higher in recipients of CS. Furthermore, this risk is most likely dose-dependent. For example, in one study, a daily dose of 10 mg of Prednisolone or more was associated with an odds ratio (OR) for an SI of 4.70, whereas a dose of 1-4.5 mg per day was associated with an OR of 2.57 [9]. Initial use of CS at first presentation may be unavoidable, but scope to wean the dose of CS should be explored, as a matter of priority, once a satisfactory response to synthetic DMARD or biologic therapy has been achieved. The minimum safe dose of CS is unknown. Indeed, in respect to SIs, there may be no safe minimum, but until more definitive data is available, a dose of 3 mg/day may represent a reasonable compromise target for maintenance of lower disease activity and at the same time minimization of SI risk [64,65].

Doses of biologic agents

The dose of any therapeutic agent should be periodically reviewed. For some biologic agents, where there is dose flexibility, lower SI risks have been convincingly demonstrated with lower doses of the biologic agent. For example, for Infliximab (INX), a 3 mg/Kg dose confers less risk than 6 mg/Kg and for Adalimumab (ADA), 40 mg every other week (EOW) confers less risk than 40 mg qw. Similar observations have been made for Tocilizumab (TCZ) where 4 mg/kg was found to confer less SI risk than 8 mg/kg [46]. Where SI risk is a major concern and disease control will allow, reduced doses of DMARDs in general, including bDMARDs, should be considered or monotherapy with a bDMARD should be preferred.

Vaccination

Pneumonias and lower respiratory tract infections in general are the most common SIs in all RA patients irrespective of biologic or synthetic DMARD therapy. Pneumococcal vaccination should be advised, unless contra-indicated, and follow-up post-vaccination serology performed to confirm adequate immunity. When it becomes more widely available/accessible, the new vaccination serology performed to confirm adequate immunity. Biologic or synthetic DMARD therapy. Pneumococcal vaccination in those with RA with undetectable MBL. The treating clinician should consider determining the MBL concentration in advance of commencing CS, sDMARD or bDMARD therapy, as this information taken together with age and CS usage will inform decision making in respect to the nature and risks of therapy.

Conclusion

In conclusion, SIs are far more common in RA than in the general population, CS are associated with an appreciable increase in SI risk (5 fold at doses of 10 mg per day or more), most commonly used and currently favored synthetic DMARDs confer a small or no risk, biologic DMARDs confer moderate risk in the first year of therapy and then a diminishing risk thereafter, and higher dose biologic or combination biologic therapy should be avoided since the serious infection risk is unacceptably high. Combinations of CS and bDMARDs or of sDMARD and bDMARDs should be used with caution in those with a track record for one or more SIs and perhaps also in the elderly. Undetectable MBL is a major risk factor for SI in RA, comparable to Prednisolone 10 mg per day or more and measurement thereof will inform SI risk stratification.

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