Paediatric Respiratory Reviews 14 (2013) 236–241

Contents lists available at SciVerse ScienceDirect

Paediatric Respiratory Reviews

CME article

Pulmonary Complications of Biological Therapies in Children and Adults with Rheumatic Diseases

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EDUCATIONAL AIMS

- To present a literature review of the pulmonary toxicity of biologic drugs
- To discuss both infections and non-infectious respiratory complications associated with biologics
- To illustrate the complexities of decision making when prescribing biologics for rheumatic diseases
- To emphasise the importance of longitudinal follow-up of all patients prescribed biologics

ARTICLE INFO

Keywords:
Biologics
bDMARDS
Pulmonary
Safety
Complications
ILD

SUMMARY

The management of rheumatic conditions, including those occurring in children, has improved dramatically over the last decade following the introduction of biologic disease-modifying anti-rheumatic drugs (bDMARDS) into the therapeutic arsenal. The benefits have been realised in multiple aspects of disease including signs and symptoms, bone and cartilage destruction, disability and quality of life. Overall, bDMARDS have an acceptable safety profile in the short to medium term in adults and children, however, that following longer term use remains unclear. As these drugs target key signalling molecules and cells of the immune system, adverse events are not unanticipated. In this review we will discuss pulmonary complications of biologic therapies used in the management of rheumatic diseases in both children and adults.

INTRODUCTION

Understanding of the immunopathogenesis of rheumatic diseases, including those occurring in children, has advanced greatly over the last two decades. This together with an increased appreciation of cell biology and the development of novel genetic techniques has led to the development of therapeutic molecules capable of specific targeting of the immune system. Consequently, there has been a rapid increase in the use of bDMARDS to treat autoimmune disease. Currently, nine of these are licensed for the treatment of rheumatoid arthritis (RA) in Europe and the USA (Table 1). Of these, four have been approved for the management of juvenile idiopathic arthritis (JIA): etanercept, adalimumab, abatacept and tocilizumab.[1,2]

It is now hard to imagine a therapeutic landscape devoid of these agents as they have led to unprecedented improvements in clinical and functional outcomes, particularly in patients with RA and JIA. As with any medication however potential toxicity is paramount to determine the risk/benefit ratio and hence position in the therapeutic algorithm. This is critical in the case of bDMARDs where the target of the intervention lies within complex biological systems responsible for fundamental physiological functions. In relation to this, the safety of these drugs has been tested in numerous clinical trials leading to the overall consensus that they are well-tolerated with an acceptable toxicity profile. Nevertheless, randomised controlled trials are insufficient to detect rarer complications and all side effects of concern.

The reasons for this include ascertainment bias in enrolled trial patients, population homogeneity, short trial duration (usually 6 months), and a relatively small sample size. Similarly, restricted entry into clinical trials based on comorbidities, i.e exclusion of significant or potentially life-threatening medical conditions, as well as restricted concomitant medications, results in a unique population with lower risks of adverse events than in the general population.[3]

Post-approval adverse event reporting is one strategy to circumvent these limitations with a prime example being the

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http://dx.doi.org/10.1016/j.prrv.2012.12.007

Table 1
Salient features of currently licensed biologic therapies in inflammatory arthritis.

Generic name (trade name)	Manufacturer	Molecular Structure	Year of first approval	Half life	Paediatric Dosage	Current license
Tumour Necrosis Factor α inhibitors						
Etanercept (Enbrel)	Pfizer (formerly Wyeth)	Recombinant human soluble anti TNFα receptor fusion protein	1998	70-132 hrs	0.8mg/kg weekly or 0.4mg/kg twice weekly	RA, PsA, AS, pJIA (≥2 yrs age)
Infliximab (Remicade)	Schering Plough (MSD)	Chimeric monoclonal antibody to TNFα	1999	9.5 days	NA	RA, AS, PsA
Adalimumab (Humira)	Abbott	Recombinant human monoclonal antibody to TNFα	2002	10-20 days	<30 kg: 20 mg fortnightly ≥30kg: 40 mg fortnightly	RA, AS, PsA, pJIA (≥4 yrs age)
Golimumab (Simponi)	Schering Plough (MSD)	Fully human monoclonal antibody to TNFα	2009	7-20 days	NA	RA, AS, PsA
Certolizumab Pegol (Cimzia)	UCB	Pegylated Fab fragment recombinant humanised anti TNFα antibody	2009	14 days	NA	RA
T cell co- stimulation blockade						
Abatacept (Orencia)	BMS	Fusion protein of an immunoglobulin and extracellular domain of CTLA-4	2011	16.7 days	10mg/kg 0,2,4 weeks then 4 weekly	RA, pJIA (≥6yrs age)
Interleukin-1 inhibition						
Anakinra (Kineret)	Amgen	Recombinant IL-1 receptor antagonist	2001	4-6 hrs	NA	RA
B cell depletion						
Rituximab (Mabthera)	Roche	Chimeric monoclonal antibody to CD20 B cells	1997	8.6 days	NA	RA
Interleukin-6 inhibition						
Tocilizumab (Roactemra)	Roche	Humanised monoclonal antibody to IL-6 receptor	2010	160+/- 34 hrs	<30kg: 12mg/kg fortnightly ≥30kg: 8mg/kg fortnightly	RA, sJIA (≥2 yrs age)

RA rheumatoid arthritis, PsA psoriatic arthritis, AS ankylosing spondylitis, pJIA polyarticular juvenile idiopathic arthritis, sJIA systemic juvenile idiopathic arthritis, NA not approved in JIA.

discovery of anti-TNF therapy leading to reactivation of latent tuberculosis infection.[4] Two main sources of such information are post-approval databases such as those run by the Food and Drug Administration (FDA) [www.fda.gov] and European Medicines Agency (EMA) [www.ema.europa.eu] and long term registries eg. British Society of Rheumatology Biologics Register (BSRBR) [www.medicine.manchester.ac.uk/arc/BSRBR/] and the National Databank of Rheumatic Disease (NDRD) [http://www.arthritis-research.org/]. It is important to remember that such data may be limited by substantial underreporting, incomplete and unverifiable data acquisition, and ascertainment bias.

As the lion share of information regarding bDMARDs use is in adults, our review focuses on pulmonary complications of these therapies in this group however paediatric data has been included where available.

TUMOUR NECROSIS FACTOR α ANTAGONISTS

Following the identification of the pivotal role played by the proinflammatory cytokine TNFα in the immunopathogenesis of RA, research was directed at blocking this molecule in a targeted fashion. TNFα inhibitors thus became the first rationally based intervention in RA and were the first recombinant proteins used for treating this condition.[5] Currently five biologics in this class have been licensed by the FDA and EMA for the treatment of a variety of inflammatory musculoskeletal disorders and related auto-immune conditions. Two of these, etanercept and adalimumab, have been approved for the treatment of JIA.

Infliximab (Remicade), a chimeric monoclonal antibody directed against TNFα, was the first to be licensed for clinical use in 1999. Infliximab is administered intravenously in doses of 3–6 mg/kg bodyweight with an infusion interval of 4 to 8 weeks. Etanercept (Enbrel), a fusion protein mimicking the function of a soluble TNF receptor, prevents TNFα binding to its cellular receptor. In children etanercept is administered subcutaneously in a dose of 0.4 mg/kg (maximum dose 25 mg) twice weekly. In the USA a weekly dose of 0.8 mg/kg in one or two single doses is approved. Adalimumab (Humira), a fully humanised monoclonal antibody against TNFα, is administered subcutaneously at a dose of 20 or 40 mg (depending on weight) every other week. Recently, two further anti-TNFα agents have been licensed for RA: certolizumab (Cimzia) a PEGylated Fab fragment of a humanised anti-TNFα antibody administered subcutaneously every 2 weeks and golimumab (Simponi), another fully human monoclonal antibody against TNFα given subcutaneously once per month. Unlike the monoclonal antibodies, etanercept neutralises soluble TNFα only and does not affect membrane-bound TNFα.

Over three million patients worldwide have now received TNF antagonists for variety of conditions.[6] Long-term post marketing surveillance data and that from national registries has confirmed the acceptable safety profile of these drugs. No convincing evidence exists to suggest that one agent is better or worse than the other with regard to infection risk. A higher rate of upper respiratory infections however has been observed with all anti TNFα agents compared with placebo in clinical trials, most notable within the first three months of treatment.[3] Although the rate of serious infections is comparable clinical trials are not usually powered, nor of sufficient duration, to detect an increased rate of such complications. The BSRBR has shown however that anti TNFα therapy increases the risk of serious infection two fold, particularly in the first 3–6 months of the treatment.[7] For serious infections, the number needed to harm (NNH) has been calculated at 59 (95% CI, 39–125) within a treatment period of 3 to 12 months. Conversely, a recent Cochrane review of the tolerability of biologics in RA did not detect a statistically significant difference in serious adverse events nor serious infections.[8] An outlier to this was certolizumab which appeared to be associated with a statistically significant increased risk of serious infections compared to placebo with an

odds ratio (OR) of 3.51 and NNH of 17. However the number of patients on certolizumab was lower than the other agents which may have biased the results. Infliximab was found to be associated with a higher (statistically significant) rate of discontinuation due to adverse events than other biologic agents. Studies in JIA of all three agents have also shown a higher risk of serious infections in the active arms compared with placebo.[8]

As TNFα plays a critical role in the immune response to intracellular organisms such as mycobacterium tuberculosis (TB), this has been the most common granulomatous infection observed following anti-TNFα treatment. Its incidence is influenced by age, socioeconomic status and geographic location.[9] Similarly, the onset of TB post-exposure differs significantly, with the median time of onset of 11.2 months with etanercept, whilst 61% of patients treated with infliximab developed TB within the first 3 infusions (6 weeks). More than 50% of the cases reported following anti-TNFα treatment were extra-pulmonary and most occurred in patients with a history of TB, suggesting reactivation of latent infection.[3] Some cases have occurred however in patients with no known history of TB. The risk appears to be less with etanercept possibly due to its unique construct and mechanism of action. Screening is now mandatory for latent TB infection prior to starting bDMARDS and guidelines have been developed for this.[10] The substantial reduction in TB cases almost certainly reflects this precaution. The ACR (American College of Rheumatology) recommends using the Mantoux purified protein derivative skin test with repeat testing approximately once yearly thereafter in patients who continue to receive TNFα inhibitors (level D). The appropriateness of interferon- gamma release assays for detecting tuberculosis was not evaluated although these are currently used in the UK for TB testing. The appropriateness of tuberculosis testing prior to the initiation of biologic agents other than TNFα inhibitors was not evaluated.[11]

Reports also exist of serious opportunistic infection following TNFα antagonism including reactivated histoplasmosis, listeriosis, pulmonary aspergillosis, and pneumocystis *jirovecii* pneumonia. These are rare and are dependent upon geographic factors.[12]

Interstitial lung disease (ILD) as a possible complication of anti TNFα therapy was first described in 2002[13] with multiple case reports subsequently suggesting a causal link.[14,15] A recent systematic literature review compiled 122 such cases of ILD from 35 case reports and four further publications.[16] The majority of patients had received etanercept (n=58) or infliximab (n=56) for the treatment of RA (n=108). Of 52 cases where data was available, 38% had pre-existing ILD which worsened after biologic therapy, with 63% having a history of current or previous methotrexate (MTX) use. New onset or worsening of ILD appeared between 1 week and 4 years after commencing the biologic agent (mean 26 +/-5 weeks). Complete resolution was reported in 21 (40%) cases, improvement or partial resolution in 13 (25%), and no improvement in 18 (35%). Fifteen (29%) patients died during the follow-up, the majority (70%) during the first 5 weeks after initiating biologic therapy. The overall mortality rate was around one third and was more likely in older patients and in those with pre-existing ILD. There are no reported cases of ILD in children with these agents.

The newest additions to this class of bDMARDS, golimumab and certolizumab, have been implicated in the development of ILD in adults.[17] According to the EMA 2009 Assessment Report, five cases of serious non-infectious pulmonary adverse events were observed in five phase III trials of golimumab including 1 case of ILD, 2 cases of pneumonitis and 1 case of fibrosing alveolitis. All of these occurred in patients receiving golimumab and concurrent methotrexate (MTX). Furthermore, the GO-BEFORE study, in adult patients with RA, reported 2 cases of microbiological culture negative pneumonia in the golimumab 100 mg plus MTX group. 6/502 (1.2%) patients who developed parenchymal lung toxicity were all receiving MTX. None of the 1129 trial patients on golimumab alone developed any parenchymal lung toxicity and none of the placebo group alone developed pulmonary side effects, however, 2/280 patients (0.71%) in the placebo plus MTX control group developed pneumonitis. Thus an association with MTX could not be fully excluded for all these episodes. Based upon these data, it is currently unclear if non-infectious pulmonary complications are associated with golimumab monotherapy. Golimumab is not currently licenced for use in children.

Certolizumab pegol does not possess an Fc-region therefore cell-mediated cytotoxicity is not possible. This could possibly result in a decreased risk of infection compared with the other TNF-α antibodies. Recently two case reports of certolizumab induced new onset ILD have been described however in one case the patient had been exposed to etanercept previously.[18,19] Certolizumab pegol is not licenced for use in children.

Data from BSRBR suggests that the mortality for RA associated ILD in patients on anti TNF agents is 68 deaths/1000 person years (pyrs) (95% CI 53 to 86) and 92/1000 pyrs (95% CI 50 to 155) in the DMARD control group, generating an age- and sex-adjusted mortality rate ratio (aMRR) of 1.26 (95% CI 0.69 to 2.31. With further adjustment for potential confounders, the aMRR fell to 0.81 (95% CI 0.38 to 1.73) for the anti-TNF cohort compared with the DMARD cohort.[20]

B CELL DEPLETION

The chimeric monoclonal antibody rituximab (RTX), directed against the cell surface molecule CD20, targets all stages of B cell maturation apart from early pro-B lymphocytes and plasma cells. Rituximab is licensed for use in patients with RA and is administered as two intravenous infusions 15 days apart (total dose 2 g). Rituximab however is primarily used in chemotherapeutic regimens for the management of certain haematological malignancies.[21] There have been uncontrolled studies of its use in children with JIA however it remains unlicensed for paediatric use.

Trial evidence suggests that RTX for the treatment of RA has an acceptable safety profile with 5.2 serious infections per 100 patient-years compared to 3.7 in the placebo group in the REFLEX study.[22] Despite this, a number of infections have been reported in association with its use. Respiratory events have been shown in up to 38% of patients receiving RTX including cough, bronchospasm, dyspnoea, sinusitis and rhinitis (much of which is associated with a cell lysis type syndrome at the time of infusion). Likewise, respiratory tract infections have been reported in up to 10% of patients. Overall however RTX is deemed to be at least as safe as the anti-TNFs with regard to infection risk. Reports of RTX-ILD are rare with the incidence of this complication being estimated to be 0.01–0.03% in adults.[23]

In our systematic literature review we identified 121 cases of RTX associated ILD from 65 studies.[24] The most frequent indication for RTX was haematological malignancy followed by autoimmune or rheumatic disease. In most cases RTX was administered as part of combination chemotherapy with other cytotoxic agents however in 30 cases RTX was given as monotherapy. The mean number of RTX cycles given prior to disease manifestation was 4.1 (range 1–12 cycles) where a single cycle consisted of an infusion of 375 mg/m^2 for haematological malignancies repeated every 2, 3 or 4 weeks or two 500 mg or 1000 mg IV infusions given 2 weeks apart for rheumatic conditions. The number of cycles or cumulative dose of RTX however did not appear to be related to disease occurrence or outcome. The mean time of onset, from the last RTX infusion, until respiratory symptoms or detection of radiological abnormality was 30 days (range 0–158 days), with a

median of 15 days (inter-quartile range 7–31 days). Outcome data from 99 cases revealed that 68 (69%) patients experienced full recovery mainly with corticosteroid therapy and having stopped RTX. Five (7.3%) of these recovered spontaneously. Nine (10%) patients achieved partial recovery with persistent respiratory compromise. RTX-ILD was fatal in 18 (19%) cases. Seventeen patients (18%) required mechanical ventilation either immediately or following disease progression and of these 9 (50%) died. High doses of steroids were unable to prevent death in a number of patients. Even amongst those receiving corticosteroids as part of the RTX regimen, no relationship was found for a more favourable outcome or avoidance of mechanical ventilation or death. In patients who improved in association with corticosteroid treatment symptomatic recovery was achieved within days, with radiological resolution lagging behind (weeks to months). Two of 10 patients experienced disease recurrence following re-challenge with RTX. There are no reports of ILD in children treated with RTX.

INTERLEUKIN-6 INHIBITION

Tocilizumab (TCZ) is a recombinant humanised monoclonal antibody targeting the human interleukin-6 (IL-6) receptor. It was approved for the treatment of systemic (sJIA) and polyarticular JIA (pJIA) in Japan in 2008 and is now licensed for sJIA in Europe and USA and has now been approved by NICE for this indication.[25] Tocilizumab is also licenced for the treatment of RA.

In the 6-month controlled studies using TCZ for RA, the rate of all infections and serious infections reported with TCZ 8 mg/kg plus DMARD treatment were 127 and 5.3 events per 100 patient years respectively compared to 112 and 3.9 events per 100 patient years in the placebo plus DMARD group. In the long-term exposure population, the overall rate was 108 and 4.7 events per 100 patient years respectively.[26]

In open label extension studies of TCZ in JIA patients, serious adverse events and serious infections occurred at a rate of 37 and 14.5 per 100 patient-years. The most common events were diarrhoea (3.8/100 patient-years) and pneumonia (3.4/100 patient-years) however opportunistic infections and tuberculosis (TB) were not observed.[27] It appears that a potential advantage of TCZ over TNF inhibitors is that reactivation of latent TB does not appear to be an issue as IL-6 has little, if any role in granuloma formation.[26] It is important to note however that TB screening was undertaken in all patients included in the TCZ trials and current practice is to screen for TB in all patients starting biologic therapy.

There are no reports of ILD in JIA population following the use of TCZ. In our review of adult use, 12 cases of new onset non-infectious pulmonary adverse effects were identified. These include three cases of culture negative pneumonias, six cases of lung toxicity during three large RCTs and three cases of ILD. In addition, there has been one case report of fatal exacerbation of RA related ILD.[17]

T CELL CO-STIMULATION BLOCKADE

Abatacept is a CTLA4–Ig fusion protein that binds to CD80/CD86 on antigen presenting cells blocking its interaction with CD28 on T cells thereby preventing T-cell activation. Abatacept is given 10 mg/kg intravenously biweekly at weeks 0, 2, 4 and then every 4 weeks. It has been licensed for treatment of polyarticular JIA patients of 6 years or older refractory or intolerant to TNF inhibitors. Recently, a subcutaneous preparation has been approved for use in adults.

Combined data from 5 RCTs in adults has suggested that the risk for serious infection is 3% compared to 1.9% in the placebo groups.[28] Interestingly a Cochrane safety review suggested that abatacept had a better safety profile than most other biologics.[8] Paediatric data also confirms the favourable tolerability profile of abatacept with comparable numbers of adverse events on abatacept to those on placebo.[29]

Although there is an established association between abatacept and exacerbations of chronic obstructive pulmonary disease (COPD), our literature search did not identify any other cases of non-infectious pulmonary toxicity, in particular ILD.[17] Similarly, there are no such reports of ILD occurring in children.

INTERLEUKIN-1 INHIBITION

The proinflammatory cytokine IL-1 appears to be key in the development of sJIA. Currently three different biologic inhibitors of the IL-1β pathway are available: anakinra, an IL-1 receptor antagonist, canakinumab, a human IL-1β antibody, and rilonacept, an IL-1 receptor fusion protein.

Anakinra is an IL-1 receptor antagonist that binds competitively to the IL-1 receptor thereby blocking the biological activity of IL-1. In a placebo-controlled trial in patients with polyarticular JIA no benefit was seen with anakinra treatment over placebo.[30] However, the effectiveness of anakinra in sJIA has been shown to be superior to those with other categories of JIA.[31] Anakinra therefore has recently been proposed as a first steroid sparing treatment if systemic features are prominent.[11] To date anakinra is only approved for the treatment of RA however frequent injection site reactions, inferior efficacy and a worse side effect profile have limited its usefulness in RA.

Similar to the adults' population the use of anakinra in sJIA has been associated with an increased risk of infectious complications.[31] There have been seven reports of ILD developing in RA patients having received anakinra, three of which were fatal.[28] There has been one report of pulmonary fibrosis in a child during the long-term treatment of 23 patients aged 5–20 years with rilonacept in an open-label extension study.[32] There are no such reports with the use of anakinra and canakinumab.

DISCUSSION

The introduction of biologics into clinical practice has led to a seachange in the outcome of patients with a variety of autoimmune diseases. Although the overall safety profile of biologic agents is acceptable, rare adverse events have been reported including ILD. Our review has shown that in clinical studies, especially in the major pre-licensing trials, evaluation of ILD as an adverse effect is frequently inadequate.[28] A variety of factors contribute to this underestimation including the rarity of the complication, the strict selection of patients for clinical trials and misdiagnosis of ILD. Hence post-marketing reporting provides most of our knowledge in this area suggesting that this may be more common, more severe and associated with a poorer prognosis than initially reported. The true incidence of ILD may be higher still as mild disease may be sub-clinical or attributed to infection or progression of the underlying disease and hence remain unreported.

It is well recognized that patients with rheumatic diseases, such as RA, are at an increased risk for non-infectious pulmonary complications including ILD.[33,34] The prevalence of ILD in patients with recent onset RA has been reported to be as high as 8.2% and this feature adversely affects survival accounting for up to 10% of RA-related deaths.[35] In juvenile rheumatic diseases the rate of interstitial pneumonitis has been reported between 1% and 14% mainly in juvenile SLE.[36] In addition children with JIA have been shown to have significantly deranged pulmonary function tests compared to normal controls.[37] Reports have suggested an

inverse correlation between lung function parameters in children with JIA and the rheumatoid factor titre, ESR and disease duration ($p < 0.01$).[37]

The exact incidence of non-infectious pulmonary complications associated with JIA is unknown. Some cases may present *de novo* with isolated pulmonary disease, which suggests that the lung may be involved with the initial immune dysregulation that precedes the systemic inflammatory response. How disease modifying therapies regulate this inflammatory response and their relationship to the development and exacerbation of ILD is unclear, as is the role of bacterial, viral and fungal infection.

Drug-induced pulmonary toxicity has been described for conventional DMARDs, particularly MTX and more recently with TNFα antagonists.[16] Pre-existing parenchymal lung disease, especially usual interstitial pneumonia (UIP), has been proposed as an additional risk factor for this complication.[38] It appears that the newer bDMARDS are also associated with non-infectious pulmonary complications, principally ILD, occurring in the context of rheumatic diseases.[17]

The mechanism of lung injury that leads to the development of ILD remains to be elucidated. Interestingly TNFα inhibition would be expected to benefit RA-associated ILD as it has been implicated as a pivotal cytokine in the pathogenesis of pulmonary fibrosis via the modulation of TGFβ, fibroblast proliferation and matrix metalloproteases.[39,40] In addition, blocking TNFα abrogates bleomycin induced pulmonary fibrosis in animal models.[41] Conversely, global TNFα blockade may promote cell lysis, leading to the release of macrophage derived proteolytic enzymes that injure the epithelium and potentiate the fibrotic cascade.[42] Furthermore, perturbing the actions of TNFα may modulate the pro-inflammatory cytokines IL-1 and interferon−γ to create an environment that favours fibroproliferation and extra-cellular matrix deposition. This is supported by the observation of significantly elevated levels of IL-1 receptor antagonist (IL-1Ra) in the broncho-alveolar lavage from patients with pulmonary fibrosis and in those developing a bronchiolitis obliterative syndrome following lung transplantation.[43] This observation may be relevant in cases of ILD following IL-1 inhibition.

Prolonged B-cell depletion (as in the case of RTX) may interfere with lymphocyte crosstalk causing cytotoxic T lymphocyte (CTL) dysregulation, leucostasis in the pulmonary circulation or release of inflammatory cytokines and cytotoxic substances thereby promoting lung damage.[24] Overall however, the precise immunopathogenesis of biologic associated ILD remains unclear.

CONCLUSION

Biologics are now well established as effective therapies for a variety of rheumatic and autoimmune diseases including JIA. Respiratory tract infection and ILD appears to be associated with several of these agents. However, the risk in children is unclear. These complications should be suspected in any patient who develops respiratory symptoms or new radiographic changes whilst receiving biologic agents.

FUNDING SOURCE

Cambridge Arthritis Research Endeavour (CARE)

CONFLICT OF INTEREST

Dr M Nisar has no conflict of interest.

Dr A Ostor has received support from (including attendance at conferences), undertakes clinical trials and acts as a consultant to Roche, Chugai, MSD, Abbott, Pfizer, BMS & GSK.

RESEARCH DIRECTIONS

- Better understanding of the pathogenesis of interstitial lung disease occurring in rheumatic diseases
- The immunopathobiology of the non-infectious pulmonary complications associated with biologics
- Development of improved therapies with reduced toxicity
- Improved reporting systems to detect rare pulmonary complications of biologic drugs

PRACTICE POINTS

- Biologic agents have dramatically altered the outcome of rheumatic diseases
- Overall safety profile of these agents is acceptable
- Risk of infections is higher in patients receiving bDMARDS especially in the first six months of treatment
- Non-infectious pulmonary complications especially interstitial lung disease have been associated with several biologics

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Educational Questions

1. With regards to infections associated with biologic agents, which of the following statements is true?
a. Upper respiratory tract infections are one of the commonest adverse events
b. Most infections are life threatening
c. Risk of infection remains the same irrespective of the duration of treatment
d. Comorbidities do not impact the outcome of infections
e. Concomitant therapy does not influence the relative risk of infections
2. Which of these agents is a CTLA4–Ig fusion protein (that binds CD80/CD86 on antigen presenting cells blocking the interaction with CD28 on T cells) thereby preventing T-cell activation?
a. Tocilizumab
b. Abatacept
c. Anakinra
d. Infliximab
e. Canakinumab
3. Development of ILD has been associated with all these agents EXCEPT:
a. Rituximab
b. Anakinra
c. Golimumab
d. Abatacept
e. Rilonacept
4. Regarding rituximab associated ILD which of the following statements is true?
a. It is much more frequent than in anti-TNF associated ILD
b. It is more common in children
c. Most cases are in the context of haematological malignancies
d. Cumulative dose exposure is directly associated with worse outcome
e. There have been no fatalities associated with this complication
5. Which of the following agents is approved for the treatment of JIA?
a. Anakinra
b. Rituximab
c. Tocilizumab
d. Adalimumab
e. Canakinumab