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Safety evaluation of Adalimumab in Immune-Mediated Inflammatory Disorders: a rheumatological point of view

Abstract

Immune-Mediated Inflammatory Disorders (IMIDs) are systemic conditions which arise secondary to complex immune mechanism defects and can affect many organs. While previous therapies based on steroids and immunosuppressive agents had a poor risk/benefit balance, TNFα specific inhibitors such as adalimumab have revolutionised the course of many diseases and patient outcomes. However, concerns were raised regarding the increased risk of infectious diseases and neoplasia due to potential prospective loss of immune control. This is especially true when considering that IMIDs concerns elderly/frail populations, with multiple co-morbidities, organ damage and often long-term steroid therapy.

Now prescribed for more than 15 years for a diverse range of indications, long-term data highlighting the efficacy and safety are available and led to recommendations for the daily practice that will be discussed.

The efficacy of adalimumab changed the therapeutic paradigm of many diseases. Its tolerance is good and it is the most widely prescribed therapy in many IMIDs. It is now the standard of care arm in head to head trials. In the long term, adalimumab dominant role might be weakened by more targeted therapies but its varied indications among IMIDs should secure its position as an important tool in our practice for years to come.

Introduction

Adalimumab is the third licensed biologic agent, developed more than 15years ago, targeting Tumour Necrosis Factor alpha (TNFα), a key protein in the inflammation cascade [1]. The use of this fully human monoclonal antibody has expanded since its efficacy has been recognised in several immune conditions [2]. There are a total of four other licensed TNFα antibodies; infliximab, etanercept, certolizumab pegol and golimumab but adalimumab has the widest range of indications.

Two forms of TNF-α can be found in the human body; the first is a transmembrane protein that is displayed on Natural Killer (NK) and regulatory T-cells (Treg), endothelial cells and fibroblasts. Its transcription is regulated by many proteins such as NF kappa Beta (NF-κB), c-Jun N-terminal kinases, AP-1 transcription factor and nuclear factor of activated T-cells (NFAT). The second form is soluble, after having been cleaved by metalloproteases. Both forms bind bivalently to TNFR1 or TNFR2 to form multimeric complexes, which are regulated by cytokines, especially interferons. Once linked, TNF signalling induces inflammation through pro-inflammatory cytokines and apoptosis induction, prostaglandin production, leucocyte migration and fibroblast proliferation [1, 3-8].

The role of TNFα in inflammation regulation was first described in autosomal dominant auto-inflammatory diseases associated with TNFα receptor mutations, e.g. Tumour Necrosis Factor Associated Periodic Syndrome (TRAPS) [9]. Historically, TNF antagonists were developed as

chemotherapy because of their suspected tumoricidal effect. But numerous studies failed as the medication was proven more toxic than effective [10].

Body of Review

Mechanism of action

All TNFα inhibitors bind to soluble TNFα with high affinity and specificity in order to block cellular activation by TNFα [11]. Their main effect is in the clearance of excess of soluble TNFα, which decreases the production of inflammatory mediators such as interleukin-6 [12]. TNFα inhibitors can also bind to membrane TNFα-expressing cells with the same affinity [13]. They promote Treg cell expansion and regulate the balance TH1-TH17 [14-16].

Although 40mg administered every two weeks is the recommended dose in rheumatic diseases [17], it has shown rapid efficacy with good tolerance up to 10mg/kg in phase II studies. Adalimumab can be given to children over 2 years of age [18], at a dose of 20mg fortnightly when under 30kg and 40mg over 30kg (40kg for IBD).

Adalimumab has a long half-life of 15 to 19 days [19]. According to PK-PD analyses and disease activity score relationship with serum adalimumab levels, it seems that the actual recommended dose of 40mg every other week results in delays in reaching the steady state concentration and therefore clinical response and that a loading dose of 160mg could improve the speed of response [20]. This loading injection has been shown to be more efficient in the initial CLASSIC-1 study and is therefore recommended and approved in inflammatory bowel diseases (IBD) and dermatology but not for rheumatic diseases [21].

Interactions have been considered between clinical outcomes, trough levels of adalimumab (TRA), the presence of antibodies against adalimumab (AAA) and concomitant medications [22]. IMMUNOREMAR study, conducted on 54 Caucasian RA patients, showed that the presence of AAA was associated with lower TRA and therefore inferior clinical outcomes [23]. Furthermore, IMMUNOREMAR determined that, in the range of 5-8 µg/ml, TRA was predictive of clinical response without additional response over 8µg/ml, implying a possible reduction of the frequency of administration if drug levels are higher [24]. Chen et Al. followed for 24 weeks 64 RA patients, either on remission or LDA, after halving adalimumab dose. They confirmed that high TRA patients have a better outcome after biologic treatment tapering but also that patients with AAA see their TRA and outcomes distinctly decline [25]. Recently, Emery *et Al.* showed that AAA against TNF inhibitors were associated with reduced clinical efficacy [26]. The PREMIER study revealed a better clinical outcome if adalimumab was prescribed with methotrexate [27, 28]. IMMUNOREMAR completed this statement by showing that this effectiveness of the combination therapy was linked to the absence of AAA and better TRA [24]. Male gender and higher bodyweight can increase the clearance of adalimumab [21].
In Gastroenterology, the cut-off prediction value has been evaluated as ranging from 4.8 to 5.9ug/mL, with no correlation with combination therapy but a positive correlation with AAA presence. Although concomitant medication did not influence AAA and TRA, it was associated with a longer delay before treatment escalation [22]. Interestingly, a study conducted on children with Crohn's disease (CD) demonstrated that the adalimumab clearance was increased by the presence of AAA, low albumin levels and the absence of concomitant immunosuppression. Although this difference in clearance was not correlated with clinical outcomes, the TRA was [29].

Clinical applications

Adalimumab is the biologic treatment with the largest number of approved indications to date.

In rheumatology, long-term data are encouraging with good clinical results after more than 10 years of use for rheumatoid arthritis (RA) [30, 31], 2 years for psoriatic arthritis (PsA) [32], 3 years for ankylosing spondylitis (AS) [33-35], axial spondyloarthitis (SpA) [34] and juvenile idiopathic arthritis (JIA) [36].

In rheumatology, adalimumab is indicated in severe rheumatoid arthritis that has not responded to therapy with a combination of conventional disease-modifying anti-rheumatic drugs (DMARDs). It showed better outcomes compared to methotrexate (MTX) in terms of clinical response, functional assessment, ultrasound inflammation and radiological progression [28, 30, 37]. Although studies showed better short term clinical outcomes when biologic DMARDS are started earlier [38, 39], long term outcomes seemed to be similar after treatment escalation [38]. A study on poor prognosis RA patient showed less radiological damage after one year when TNF inhibitors were prescribed as a first line treatment[40] Results on larger scale in the PREMIER and DE019 studies agreed with these results but they have been doubted by Landewe *et al.*, regarding population bias and robustness of the data [41].

In Gastroenterology, it is recommended for Ulcerative Colitis (UC) and CD in adults and children and has proven long-term efficacy of 4 years for CD [42, 43]. In Dermatology, its clinical efficacy is recognised for plaque psoriasis, suppurative hidradenitis and psoriasis (Pso) with a 4.5 years sustained remission in more than 50% of patient [44]. It is also indicated in severe and resistant uveitis [45, 46].

Other potential indications (unapproved) include sarcoidosis [47], severe intestinal, rheumatologic and ocular manifestations of Bechet's disease [48, 49], conglobate acne [50] and SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome [51, 52]. It is also proven to ameliorate extra-intestinal manifestations of IBD [53, 54].

Safety evaluation

The frailty of the population treated with adalimumab has to be taken into consideration particularly with respect to previous and concomitant immune-suppressive therapies, older age, and chronic inflammation. Thus comparator/control groups are required. Burmester *et al.* published 2 reviews on adalimumab safety, analysing data of a first sample of more than 23,000 patients (across all indications, published in 2013) [55], then a second of 15,000 (related to RA, published in 2017) [56].

Mortality

Mortality rates are globally increased in inflammatory diseases, due to complications from chronic inflammation levels and cardio-vascular events [57, 58]. Regarding mortality rates on adalimumab however, studies showed no deaths in JIA patients, fewer than expected in RA patients, (0.75; IC 0.63-0.88) AS patients (0.14; IC 0 – 0.78) and Pso patients (0.32; IC 0.14 – 0.63) for age-sex matched

population, whilst they were as expected in PsA patients (0.34; IC 0.04 – 1.24) and CD (0.45; IC 0.15-1.06) [55].

Infections

In the GISEA register [59], where 2769 adult patients with long-standing RA and treated with TNFα inhibitors were followed-up for an average of 9 years, 18.6% of patients with adalimumab developed a serious infection [59]. Factors associated with an increased risk of infection in RA patients receiving biologic therapy have been identified. These include extra-articular disease and certain comorbidities (chronic lung disease, alcoholism, organic brain disease, and diabetes mellitus) lymphopenia and neutropenia [60-62]. In TNFα antagonist treated patients, only the use of concomitant steroids, advanced age and the type of biologic therapy were identified as risk factors for infection [59]. Some studies showed an increased risk of infection in the first 6 months of adalimumab or etanercept use [63, 64], but these results were not found in Burmester *et al.'s* review [55].

Serious infections

In 2013, the most commonly reported serious infectious events were cellulitis and pneumonia in RA, appendicitis and herpes in JIA, urinary tract infections in PsA, cellulitis in skin psoriasis, gastroenteritis and pneumonia in CD [55]. These infections led to discontinuation of the medication in 28-32% of the patients with RA or CD compared to 18-24% for other indications [55].

In 2018, the United Kingdom registry (BSRBR-RA cohort), included almost 20,000 patients with 46 771 patient years of follow-up [65]. The serious infection incidence for all biologics was 5.51 events/100 patient years. The incidence rate of serious infection with adalimumab (5.42%) was similar to the other TNFα inhibitors (infliximab, etanercept, golimumab and certolizumab pegol). In comparison, rituximab and tocilizumab showed higher rates of serious infection. This difference was no longer significant for rituximab after analysis adjustment for age, disease length and number of previous treatments. This study also showed a mortality rate that increased from 0.84% to 10.4% in the year following a serious infection [65], clearly this relationship is a complex one.

Opportunistic infections

Serious opportunistic infections in patients receiving adalimumab occur in less than 0.1 events per 100 patient-years [55]. Tuberculosis reactivation from its latent form is the most common opportunistic infection described. Before systematic screening and prophylactic treatment, the rate of reactivation was 1.5 events/100 patient years. Since 1999, this rate has decreased sharply to 0.2 events/100 patient years [55].

Many case reports have described various atypical infections in patients treated with biologic therapy. The most common pathogens include mycobacteria species, nocardia species, listeria

monocytogenes, herpes simplex and zoster viruses (HSV and HZV), varicella zoster (VZV), cytomegalovirus (CMV), leishmania species, pneumocystis jiroveci, aspergillus, histoplasma, candida and legionella [61, 62, 66, 67]. In the French RATIO cohort, following 3 years of data collection of more than 50.000 patient-years, regardless of the underlying inflammatory condition, 45 patients developed an opportunistic infection (tuberculosis excluded) in which 23% required intensive care treatment [61].

Some opportunistic infections such as legionellosis may occur sooner with monoclonal antibody biologic therapies (i.e. adalimumab and infliximab) than with other biologic [62, 67]. By contrast, in a United States retrospective analysis between 2004 and 2011, Herpes zoster (HZ) infection risk was not influenced by the type of biologic treatment [68].

A meticulous medical history regarding infections' risk is important before the introduction of biologic therapies with a particular attention to tuberculosis, hepatitis B and C [69]. The 2015 ACR recommendations for tuberculosis screening tests previous to biologic treatment initiation suggest performing either a Mantoux test or a Quantiferon test (interferon-gamma release assay (IGRA)). The latter is preferred for patients with a history of BCG vaccination. In the case of a positive result, chest X-Ray (followed by microbiologic analysis if positive) will define the necessity for a pre-treatment for latent or active disease in consideration with the appropriate specialists. A delay of 1 month after anti-tuberculosis treatment is recommended [70, 71]

In the Mayo Clinic between 1996 and 2004, after 657 joint replacements in RA patients, data revealed an infection rate of 3.7% [72, 73]. Revision arthroplasty, previous joint infection of the replaced joint and operation duration were all shown to increase the risk of prosthesis infection. Discontinuation of corticosteroids and concomitant medication did not show any statistically significant increase in infection risk [74]. The relationship between the length of biologic treatment and risk of prosthesis infection requires more data [72]. While recommendations differ from one country to another, a common recommendation is to withhold biologic treatment prior to elective surgery of at least one cycle of the medication [73, 75].

Induction of autoimmunity

Several studies showed the presence of adalimumab induced auto-antibodies (Ab) in patients treated with TNF inhibitors; mainly anti-nuclear Ab (ANA) but also at a lower level anti-double stranded Ab (dsDNA), rheumatoid factor (RF) and anti-CCP Ab [76, 77]; with a higher prevalence of induced ANA for infliximab than adalimumab [76]. Concomitant medications did not influence the development of these auto-Ab. These finding were not systematically associated with a symptomatic auto-immune disease and independent of therapeutic response, therefore questioning the usefulness of systematic ANA analysis without clinical features [76].

Induced immune diseases are expected to be less than 0.1% patient years [55]. Nearly 50 different diseases have been described, mainly in case reports [78]. Focusing on renal autoimmune induced disorders, a prospective study did not find any predictive markers of auto-immune changes, while others have found that the presence of anti-nucleosome antibodies is predictive of ANA [79, 80].

Malignancies

Across all conditions, the risk of malignancy in IMID is proven to be higher than the control population [81, 82].

In Burmester et Al.'s meta-analysis, events were reported at a rate of 0.7/100 patient years for overall malignancies, 0.1/100 patient years for lymphoma and 0.2/ 100 patient years for non-melanoma skin cancers. No events were reported in JIA trials with a follow-up of 6 years [55].

Cancer risk could be influenced by the disease itself, the type of cancer and the concomitant therapy, all of which need to be controlled for when comparing data.

While registers grouping patients across all indications and all TNF inhibitors did not identify an overall increase in cancer risk among IMID patients [83-85], with the exception on skin cancers in IBD in the American Register [86]. Data suggests an overall increased risk of cancer when thiopurines based immunomodulatory drugs are used in IBD [85], as well as an increased risk of non-melanoma skin cancer when phototherapy was used in psoriasis patients [87].

In RA, the British Society for Rheumatology Biologics Register (BSRBR)-initially created to have the ability to detect a 2-fold increase in lymphoma), analysed data of almost 12,000 patients, representing more than 52,000 patient years, and did not find this difference [85, 88]. These results are consistent with a nationwide Taiwanese cohort in 4400 patients, which even showed a decrease in non-haematological malignancies when compared to non-biological treatments alone [89].

In a global American study which grouped almost 40,000 patients across all indications for TNF inhibitors, no increase in cancer risk has been identified in the early years of treatment [83]. The risk of recurrence has also been evaluated. Following patients who had suffered from breast cancer, no difference was highlighted between TNF and non-TNF treated patients, knowing that patients started the biologic with a median of 9 years of remission [90]. Similar overall cancer results were found in a small retrospective study on 333 IBD patients [91]. In the German register RABBIT, the recurrence rate was insignificantly increased with an interval of 9 years before the relapse diagnosis [92].

With all these discrepancies in the results and following the tumour relapse rate of immunosuppressed patients after organ transplantation – which showed that the risk of relapse after 5 years was down to 13% after 5 years - it is recommended to start biologic treatments only after 5 years of remission [93].

In JIA, the overall risk of cancer is increased irrespective of treatment [81].

Allergic reactions

Local and systemic allergic reactions have been described such as urticaria, rhinitis angioedema and anaphylaxis [94, 95]. Some authors report the success of switching to adalimumab after allergic reaction due to infliximab [96]. Allergic reactions usually lead to a medication change, but desensitization was a success in a number of cases [97].

Rare events

Demyelinating diseases, auto-immune phenomena as described above, haematologic toxicities and congestive heart failure (CHF) represent less than 0.1 events per 100 patient-years, except in RA where CHF rates are up to 0.2 patient years. New onset of psoriasis also appears in less than 0.1 per 100 patient years [55].

Vaccination

Patients receiving TNF blockers still generate a good humoral response but lower than for healthy patients [98]. Non-live vaccines such as Influenza, pneumococcal and hepatitis B vaccine, (as well as recombinant vaccines like papilloma virus vaccine) should be administered (according to EULAR recommendations) [70, 99].

Live vaccines such as shingles and yellow fever are contraindicated in adult and children after the start of the medication [100]. Therefore Varicella Zoster Virus vaccination is recommended before the start of the treatment for children without vaccination history and patients over 50 years old [69, 70, 100]. Herpes zoster vaccine is not recommended, although a new killed vaccine will likely change this recommendation.

Post-marketing data

Adalimumab is one of the biologics with the largest data sets for safety and efficacy. While safety data were already reassuring in pre-marketing trials, real life data confirmed these findings [55, 56].

Safety in special populations, including pharmacogenomics data

In the elderly

In a 2011 study, patients over 65 years old had an increased independent risk but no relative risk of infection when treated with anti-TNF antibodies, even when taking into consideration other treatments like steroids and methotrexate [63].

In childhood

RESEAT and IMAGINE are two studies that showed comparable safety to adults' use [101, 102]. A positive correlation exists between concentration level and response to treatment in children with moderate to severe Crohn's disease [29]. Steroid sparing could partially explain an increase in growth in treated children [103].

Pregnancy

Current data on RA showed no difference in child malformations in 153 pregnancies compared to RA controls, but only 44% pursued the treatment throughout pregnancy [56]. Gastroenterologists' data on 212 patients with CD showed also no difference [104].

In IBD, it is recommended to continue anti-TNF therapies because of the risk of relapse, in the situation of a mild disease, then discontinuation can be tried at 24weeks of amenorrhea (WA) [105]. In rheumatic diseases, it is not recommended but appears reasonably safe to use until 24 WA [106]. Among the TNFα inhibitors, only Certolizumab Pegol has a PEGylated Fc domain that prevent it to be transported across the placenta [107].

HIV patients

No recommendations have been established since no randomised controlled trials have been conducted to date. A review of case-reports suggests that treated patients with stable CD4 counts could be treated with anti-TNF therapies, with monthly monitoring of $CD4^+$ levels [108].

In patients with renal insufficiency

Adalimumab clearance is not affected by glomerular dysfunction and can be administered without dose reduction in patients with renal impairment, even in haemodialysis [109].

Conclusion

Since Adalimumab has been prescribed routinely for patients differing greatly in terms of age, co-morbidities, disease indication, combination therapy and previous therapy, there is a large body of evidence to support its safety.

Even if current safety data are relatively reassuring regarding infectious risk, the frailty of the population and complexity of IMIDs and their management have to be taken into account. Although the rate of serious and opportunistic infection is similar to the other TNFα inhibitors, it is significantly higher than in the normal population. Vaccination (with the exception of live vaccines), screening tests for tuberculosis and hepatitis as well as careful clinical follow-up remain essential in usual care.

The rate of malignancies is increased in IMID. TNF inhibitors use did not show an increase in solid of haematological neoplasms, but some data indicate an increase in non-melanoma skin cancers in psoriasis and IBD, highlighting the importance of annual screening and prevention. Recurrence of a past cancer is not significantly increased but data shows some discrepancies. It is therefore recommended to wait 5 years after tumour remission before starting a TNFα antagonist. Adalimumab tolerance profile in special populations is excellent, its use is authorised after 2 years old and in the elderly, with renal impairment and during haemodialysis, and it is accepted until the 24th week of pregnancy. The risk of adverse events, especially infectious, is correlated with the severity of the IMID, comorbidities and previous treatment.

Expert opinion

Targeting TNF-alpha has produced the most significant improvements in rheumatology since the discovery of methotrexate[110]. TNF inhibitors such as adalimumab have modified the therapeutic paradigm, becoming a corner stone in the management of many inflammatory diseases. Although its cost currently limits its use to active and severe diseases, its efficacy in early diseases has been proven and the timing of its use could be modified in the future [38].

Being the top-selling monoclonal agent, numerous data has been gathered across diverse conditions and are reassuring in terms of malignancies and tolerance in frail populations. Serious and opportunistic infections, although rare, must nonetheless be kept in mind. The inflammation cascade has an important role in infection and neoplasm control, any newly designed therapies that target the inflammation cascade have the potential for serious adverse events. Long term data will be required before being considered as safe as adalimumab.

Since its excellent efficacy and tolerance profile in short and long-term data have been proven, adalimumab has become the control group drug in many new drug trials [98].

Nevertheless, our therapeutic arsenal is constantly widening and improving, giving a hope for future personalized treatment adapted to each patients' characteristics. In the long term, adalimumab dominant role might be weakened by more targeted therapies but its varied indications among IMIDs should secure its position as an important tool in our practice for years to come.

Drug Summary Box

Drug name: adalimumab

Phase: IV

Indications: rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, axial spondyloarthitis, juvenile idiopathic arthritis, Ulcerative Colitis, Crohn's disease in adults and children, plaque psoriasis, suppurative hidradenitis, psoriasis, uveitis.

Pharmacology description/mechanism of action: TNFα inhibitors bind to TNFα in order to block cellular activation, inducing a decrease in the production of inflammatory mediators

Route of administration: sub-cutaneous

Chemical structure: human monoclonal antibody (1330 amino acids, 148kD)

Pivotal trial(s) related to clinical safety:

Burmester, G.R., et al., *Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease.* Ann Rheum Dis, 2013. **72**(4): p. 517-24.

Burmester, G.R., et al., *Adalimumab long-term safety: infections, vaccination response and pregnancy outcomes in patients with rheumatoid arthritis.* Ann Rheum Dis, 2017. **76**(2): p. 414-417.

BIBLIOGRAPHY

1. Kohase, M., et al., *Induction of beta 2-interferon by tumor necrosis factor: a homeostatic mechanism in the control of cell proliferation.* Cell, 1986. **45**(5): p. 659-66.
2. Lapadula, G., et al., *Adalimumab in the treatment of immune-mediated diseases.* Int J Immunopathol Pharmacol, 2014. **27**(1 Suppl): p. 33-48.
3. Tartaglia, L.A., et al., *Tumor necrosis factor's cytotoxic activity is signaled by the p55 TNF receptor.* Cell, 1993. **73**(2): p. 213-6.
4. Fiers, W., et al., *Structure-function relationship of tumour necrosis factor and its mechanism of action.* Ciba Found Symp, 1987. **131**: p. 109-23.
5. Takeda, K., et al., *Identity of differentiation inducing factor and tumour necrosis factor.* Nature, 1986. **323**(6086): p. 338-40.
6. Trinchieri, G., et al., *Tumor necrosis factor and lymphotoxin induce differentiation of human myeloid cell lines in synergy with immune interferon.* J Exp Med, 1986. **164**(4): p. 1206-25.
7. Vilcek, J., et al., *Fibroblast growth enhancing activity of tumor necrosis factor and its relationship to other polypeptide growth factors.* J Exp Med, 1986. **163**(3): p. 632-43.
8. Choy, E.H. and G.S. Panayi, *Cytokine pathways and joint inflammation in rheumatoid arthritis.* N Engl J Med, 2001. **344**(12): p. 907-16.
9. McDermott, M.F., et al., *Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes.* Cell, 1999. **97**(1): p. 133-44.
10. Roberts, N.J., et al., *Systemic use of tumor necrosis factor alpha as an anticancer agent.* Oncotarget, 2011. **2**(10): p. 739-51.
11. Cessak, G., et al., *TNF inhibitors - Mechanisms of action, approved and off-label indications.* Pharmacol Rep, 2014. **66**(5): p. 836-44.

12. Shalaby, M.R., et al., *Endotoxin, tumor necrosis factor-alpha and interleukin 1 induce interleukin 6 production in vivo.* Clin Immunol Immunopathol, 1989. **53**(3): p. 488-98.
13. Horiuchi, T., et al., *Transmembrane TNF-alpha: structure, function and interaction with anti-TNF agents.* Rheumatology (Oxford), 2010. **49**(7): p. 1215-28.
14. Chen, X., et al., *Interaction of TNF with TNF receptor type 2 promotes expansion and function of mouse CD4+CD25+ T regulatory cells.* J Immunol, 2007. **179**(1): p. 154-61.
15. Nie, H., et al., *Phosphorylation of FOXP3 controls regulatory T cell function and is inhibited by TNF-alpha in rheumatoid arthritis.* Nat Med, 2013. **19**(3): p. 322-8.
16. Nguyen, D.X. and M.R. Ehrenstein, *Anti-TNF drives regulatory T cell expansion by paradoxically promoting membrane TNF-TNF-RII binding in rheumatoid arthritis.* J Exp Med, 2016. **213**(7): p. 1241-53.
17. van de Putte, L.B., et al., *Efficacy and safety of the fully human anti-tumour necrosis factor alpha monoclonal antibody adalimumab (D2E7) in DMARD refractory patients with rheumatoid arthritis: a 12 week, phase II study.* Ann Rheum Dis, 2003. **62**(12): p. 1168-77.
18. Kingsbury, D.J., et al., *Safety, effectiveness, and pharmacokinetics of adalimumab in children with polyarticular juvenile idiopathic arthritis aged 2 to 4 years.* Clin Rheumatol, 2014. **33**(10): p. 1433-41.
19. Weisman, M.H., et al., *Efficacy, pharmacokinetic, and safety assessment of adalimumab, a fully human anti-tumor necrosis factor-alpha monoclonal antibody, in adults with rheumatoid arthritis receiving concomitant methotrexate: a pilot study.* Clin Ther, 2003. **25**(6): p. 1700-21.
20. Ternant, D., et al., *Pharmacokinetics and concentration-effect relationship of adalimumab in rheumatoid arthritis.* Br J Clin Pharmacol, 2015. **79**(2): p. 286-97.
21. Hanauer, S.B., et al., *Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial.* Gastroenterology, 2006. **130**(2): p. 323-33; quiz 591.
22. Paul, S., et al., *Pharmacokinetics of adalimumab in inflammatory bowel diseases: a systematic review and meta-analysis.* Inflamm Bowel Dis, 2014. **20**(7): p. 1288-95.
23. Sanmarti, R., et al., *Towards optimal cut-off trough levels of adalimumab and etanercept for a good therapeutic response in rheumatoid arthritis. Results of the INMUNOREMAR study.* Ann Rheum Dis, 2015. **74**(8): p. e42.
24. Pouw, M.F., et al., *Key findings towards optimising adalimumab treatment: the concentration-effect curve.* Ann Rheum Dis, 2015. **74**(3): p. 513-8.
25. Chen, D.Y., et al., *Drug trough levels predict therapeutic responses to dose reduction of adalimumab for rheumatoid arthritis patients during 24 weeks of follow-up.* Rheumatology (Oxford), 2016. **55**(1): p. 143-8.
26. Emery, P., et al., THU0184 Impact of immunogenicity on clinical efficacy and administration related reaction in tnf inhibitors: a pooled-analysis from three biosimilar studies in patients with rheumatoid arthritis. Annals of the Rheumatic Diseases, 2018. 77(Suppl 2): p. 310-311.
27. Keystone, E.C., et al., *Longterm effect of delaying combination therapy with tumor necrosis factor inhibitor in patients with aggressive early rheumatoid arthritis: 10-year efficacy and safety of adalimumab from the randomized controlled PREMIER trial with open-label extension.* J Rheumatol, 2014. **41**(1): p. 5-14.
28. Breedveld, F.C., et al., *The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment.* Arthritis Rheum, 2006. **54**(1): p. 26-37.
29. Sharma, S., et al., *Pharmacokinetics and exposure-efficacy relationship of adalimumab in pediatric patients with moderate to severe Crohn's disease: results from a randomized, multicenter, phase-3 study.* Inflamm Bowel Dis, 2015. **21**(4): p. 783-92.

30. Keystone, E.C., et al., *Clinical, functional, and radiographic benefits of longterm adalimumab plus methotrexate: final 10-year data in longstanding rheumatoid arthritis.* J Rheumatol, 2013. **40**(9): p. 1487-97.
31. Weinblatt, M.E., et al., *Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial.* Arthritis Rheum, 2003. **48**(1): p. 35-45.
32. Mease, P.J., et al., *Adalimumab for long-term treatment of psoriatic arthritis: 2-year data from the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT).* Ann Rheum Dis, 2009. **68**(5): p. 702-9.
33. van der Heijde, D., et al., *Maintenance of improvement in spinal mobility, physical function and quality of life in patients with ankylosing spondylitis after 5 years in a clinical trial of adalimumab.* Rheumatology (Oxford), 2015. **54**(7): p. 1210-9.
34. Sieper, J., et al., *Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1).* Ann Rheum Dis, 2013. **72**(6): p. 815-22.
35. Rudwaleit, M., et al., *Effectiveness, safety, and predictors of good clinical response in 1250 patients treated with adalimumab for active ankylosing spondylitis.* J Rheumatol, 2009. **36**(4): p. 801-8.
36. Murdaca, G., B.M. Colombo, and F. Puppo, *Adalimumab for the treatment of immune-mediated diseases: an update on old and recent indications.* Drugs Today (Barc), 2011. **47**(4): p. 277-88.
37. Emery, P., et al., *Less radiographic progression with adalimumab plus methotrexate versus methotrexate monotherapy across the spectrum of clinical response in early rheumatoid arthritis.* J Rheumatol, 2009. **36**(7): p. 1429-41.
38. Nam, J.L. and P. Emery, *Is there a place for initial treatment with biological DMARDs in the early phase of RA?* Best Pract Res Clin Rheumatol, 2013. **27**(4): p. 537-54.
39. Keystone, E.C., et al., *Clinical consequences of delayed addition of adalimumab to methotrexate therapy over 5 years in patients with rheumatoid arthritis.* J Rheumatol, 2011. **38**(5): p. 855-62.
40. Quinn, M.A., et al., *Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial.* Arthritis Rheum, 2005. **52**(1): p. 27-35.
41. Landewe, R., et al., *Analysis of integrated radiographic data from two long-term, open-label extension studies of adalimumab for the treatment of rheumatoid arthritis.* Arthritis Care Res (Hoboken), 2015. **67**(2): p. 180-6.
42. Colombel, J.F., et al., *Four-year maintenance treatment with adalimumab in patients with moderately to severely active ulcerative colitis: Data from ULTRA 1, 2, and 3.* Am J Gastroenterol, 2014. **109**(11): p. 1771-80.
43. Panaccione, R., et al., *Adalimumab maintains remission of Crohn's disease after up to 4 years of treatment: data from CHARM and ADHERE.* Aliment Pharmacol Ther, 2013. **38**(10): p. 1236-47.
44. van den Reek, J.M., et al., *Predictors of adalimumab drug survival in psoriasis differ by reason for discontinuation: long-term results from the Bio-CAPTURE registry.* J Eur Acad Dermatol Venereol, 2015. **29**(3): p. 560-5.
45. Vallet, H., et al., *Infliximab Versus Adalimumab in the Treatment of Refractory Inflammatory Uveitis: A Multicenter Study From the French Uveitis Network.* Arthritis Rheumatol, 2016. **68**(6): p. 1522-30.
46. Suhler, E.B., et al., *Safety and Efficacy of Adalimumab in Patients with Noninfectious Uveitis in an Ongoing Open-Label Study: VISUAL III.* Ophthalmology, 2018.

47. Drent, M., et al., *Practical eminence and experience-based recommendations for use of TNF-alpha inhibitors in sarcoidosis.* Sarcoidosis Vasc Diffuse Lung Dis, 2014. **31**(2): p. 91-107.
48. Vallet, H., et al., *Efficacy of anti-TNF alpha in severe and/or refractory Behcet's disease: Multicenter study of 124 patients.* J Autoimmun, 2015. **62**: p. 67-74.
49. Arida, A., et al., *Anti-TNF agents for Behcet's disease: analysis of published data on 369 patients.* Semin Arthritis Rheum, 2011. **41**(1): p. 61-70.
50. Yiu, Z.Z., V. Madan, and C.E. Griffiths, *Acne conglobata and adalimumab: use of tumour necrosis factor-alpha antagonists in treatment-resistant acne conglobata, and review of the literature.* Clin Exp Dermatol, 2015. **40**(4): p. 383-6.
51. Alexis, A.F. and B.E. Strober, *Off-label dermatologic uses of anti-TNF-a therapies.* J Cutan Med Surg, 2005. **9**(6): p. 296-302.
52. Garcovich, S., et al., *Long-term treatment of severe SAPHO syndrome with adalimumab: case report and a review of the literature.* Am J Clin Dermatol, 2012. **13**(1): p. 55-9.
53. Kotaniemi, K., H. Saila, and H. Kautiainen, *Long-term efficacy of adalimumab in the treatment of uveitis associated with juvenile idiopathic arthritis.* Clin Ophthalmol, 2011. **5**: p. 1425-9.
54. Lofberg, R., et al., *Adalimumab produces clinical remission and reduces extraintestinal manifestations in Crohn's disease: results from CARE.* Inflamm Bowel Dis, 2012. **18**(1): p. 1-9.
55. Burmester, G.R., et al., *Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease.* Ann Rheum Dis, 2013. **72**(4): p. 517-24.
56. Burmester, G.R., et al., *Adalimumab long-term safety: infections, vaccination response and pregnancy outcomes in patients with rheumatoid arthritis.* Ann Rheum Dis, 2017. **76**(2): p. 414-417.
57. Libby, P., *Inflammation in atherosclerosis.* Arterioscler Thromb Vasc Biol, 2012. **32**(9): p. 2045-51.
58. Bonaccio, M., et al., *A score of low-grade inflammation and risk of mortality: prospective findings from the Moli-sani study.* Haematologica, 2016. **101**(11): p. 1434-1441.
59. Atzeni, F., et al., *Long-term anti-TNF therapy and the risk of serious infections in a cohort of patients with rheumatoid arthritis: comparison of adalimumab, etanercept and infliximab in the GISEA registry.* Autoimmun Rev, 2012. **12**(2): p. 225-9.
60. Doran, M.F., et al., *Predictors of infection in rheumatoid arthritis.* Arthritis Rheum, 2002. **46**(9): p. 2294-300.
61. Salmon-Ceron, D., et al., *Drug-specific risk of non-tuberculosis opportunistic infections in patients receiving anti-TNF therapy reported to the 3-year prospective French RATIO registry.* Ann Rheum Dis, 2011. **70**(4): p. 616-23.
62. Tsiodras, S., et al., *Fungal infections complicating tumor necrosis factor alpha blockade therapy.* Mayo Clin Proc, 2008. **83**(2): p. 181-94.
63. Galloway, J.B., et al., *Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly.* Rheumatology (Oxford), 2011. **50**(1): p. 124-31.
64. Emery, P., et al., *Association between disease activity and risk of serious infections in subjects with rheumatoid arthritis treated with etanercept or disease-modifying anti-rheumatic drugs.* Clin Exp Rheumatol, 2014. **32**(5): p. 653-60.
65. Rutherford, A.I., et al., *Serious infection across biologic-treated patients with rheumatoid arthritis: results from the British Society for Rheumatolgy Biologics Register for Rheumatoid Arthritis.* Ann Rheum Dis, 2018.
66. Downey, C., *Serious infection during etanercept, infliximab and adalimumab therapy for rheumatoid arthritis: A literature review.* Int J Rheum Dis, 2016. **19**(6): p. 536-50.

67. Lanternier, F., et al., *Incidence and risk factors of Legionella pneumophila pneumonia during anti-tumor necrosis factor therapy: a prospective French study.* Chest, 2013. **144**(3): p. 990-998.
68. Yun, H., et al., *Risks of herpes zoster in patients with rheumatoid arthritis according to biologic disease-modifying therapy.* Arthritis Care Res (Hoboken), 2015. **67**(5): p. 731-6.
69. Murdaca, G., et al., *Infection risk associated with anti-TNF-alpha agents: a review.* Expert Opin Drug Saf, 2015. **14**(4): p. 571-82.
70. Singh, J.A., et al., *2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis.* Arthritis Care Res (Hoboken), 2016. **68**(1): p. 1-25.
71. Saag, K.G., et al., *American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis.* Arthritis Rheum, 2008. **59**(6): p. 762-84.
72. Goodman, S.M., et al., *Management of perioperative tumour necrosis factor alpha inhibitors in rheumatoid arthritis patients undergoing arthroplasty: a systematic review and meta-analysis.* Rheumatology (Oxford), 2016. **55**(3): p. 573-82.
73. Goodman, S.M., *Rheumatoid arthritis: Perioperative management of biologics and DMARDs.* Semin Arthritis Rheum, 2015. **44**(6): p. 627-32.
74. Momohara, S., et al., *Prosthetic joint infection after total hip or knee arthroplasty in rheumatoid arthritis patients treated with nonbiologic and biologic disease-modifying antirheumatic drugs.* Mod Rheumatol, 2011. **21**(5): p. 469-75.
75. Goodman, S.M., et al., *2017 American College of Rheumatology/American Association of Hip and Knee Surgeons Guideline for the Perioperative Management of Antirheumatic Medication in Patients With Rheumatic Diseases Undergoing Elective Total Hip or Total Knee Arthroplasty.* Arthritis Care Res (Hoboken), 2017. **69**(8): p. 1111-1124.
76. Bacquet-Deschryver, H., et al., *Impact of three anti-TNFalpha biologics on existing and emergent autoimmunity in rheumatoid arthritis and spondylarthropathy patients.* J Clin Immunol, 2008. **28**(5): p. 445-55.
77. Takase, K., et al., *What is the utility of routine ANA testing in predicting development of biological DMARD-induced lupus and vasculitis in patients with rheumatoid arthritis? Data from a single-centre cohort.* Ann Rheum Dis, 2014. **73**(9): p. 1695-9.
78. Perez-Alvarez, R., M. Perez-de-Lis, and M. Ramos-Casals, *Biologics-induced autoimmune diseases.* Curr Opin Rheumatol, 2013. **25**(1): p. 56-64.
79. Piga, M., et al., *Biologics-induced autoimmune renal disorders in chronic inflammatory rheumatic diseases: systematic literature review and analysis of a monocentric cohort.* Autoimmun Rev, 2014. **13**(8): p. 873-9.
80. Benucci, M., et al., *Anti-nucleosome antibodies as prediction factor of development of autoantibodies during therapy with three different TNFalpha blocking agents in rheumatoid arthritis.* Clin Rheumatol, 2008. **27**(1): p. 91-5.
81. Onel, K.B. and K. Onel, *Tumor necrosis factor inhibitors and cancer in juvenile idiopathic arthritis: disentangling the web.* Arthritis Rheum, 2012. **64**(4): p. 966-9.
82. Beyaert, R., et al., *Cancer risk in immune-mediated inflammatory diseases (IMID).* Mol Cancer, 2013. **12**(1): p. 98.
83. Haynes, K., et al., *Tumor necrosis factor alpha inhibitor therapy and cancer risk in chronic immune-mediated diseases.* Arthritis Rheum, 2013. **65**(1): p. 48-58.
84. Nyboe Andersen, N., et al., *Association between tumor necrosis factor-alpha antagonists and risk of cancer in patients with inflammatory bowel disease.* Jama, 2014. **311**(23): p. 2406-13.
85. Osterman, M.T., et al., *Increased risk of malignancy with adalimumab combination therapy, compared with monotherapy, for Crohn's disease.* Gastroenterology, 2014. **146**(4): p. 941-9.
86. McKenna, M.R., D.J. Stobaugh, and P. Deepak, *Melanoma and non-melanoma skin cancer in inflammatory bowel disease patients following tumor necrosis factor-alpha inhibitor monotherapy and in combination with thiopurines: analysis of the Food and Drug*

Administration Adverse Event Reporting System. J Gastrointestin Liver Dis, 2014. **23**(3): p. 267-71.
87. van Lumig, P.P., et al., *An increased risk of non-melanoma skin cancer during TNF-inhibitor treatment in psoriasis patients compared to rheumatoid arthritis patients probably relates to disease-related factors.* J Eur Acad Dermatol Venereol, 2015. **29**(4): p. 752-60.
88. Mercer, L.K., et al., *Risk of solid cancer in patients exposed to anti-tumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis.* Ann Rheum Dis, 2015. **74**(6): p. 1087-93.
89. Wu, C.Y., et al., *The risk of cancer in patients with rheumatoid arthritis taking tumor necrosis factor antagonists: a nationwide cohort study.* Arthritis Res Ther, 2014. **16**(5): p. 449.
90. Raaschou, P., T. Frisell, and J. Askling, *TNF inhibitor therapy and risk of breast cancer recurrence in patients with rheumatoid arthritis: a nationwide cohort study.* Ann Rheum Dis, 2015. **74**(12): p. 2137-43.
91. Axelrad, J., et al., *Risk of New or Recurrent Cancer in Patients With Inflammatory Bowel Disease and Previous Cancer Exposed to Immunosuppressive and Anti-Tumor Necrosis Factor Agents.* Clin Gastroenterol Hepatol, 2016. **14**(1): p. 58-64.
92. Strangfeld, A., et al., *Risk of incident or recurrent malignancies among patients with rheumatoid arthritis exposed to biologic therapy in the German biologics register RABBIT.* Arthritis Res Ther, 2010. **12**(1): p. R5.
93. Bernheim, O., et al., *The management of immunosuppression in patients with inflammatory bowel disease and cancer.* Gut, 2013. **62**(11): p. 1523-8.
94. Campi, P., et al., *Hypersensitivity reactions to biological agents with special emphasis on tumor necrosis factor-alpha antagonists.* Curr Opin Allergy Clin Immunol, 2007. **7**(5): p. 393-403.
95. Nikas, S.N., P.V. Voulgari, and A.A. Drosos, *Urticaria and angiedema-like skin reactions in a patient treated with adalimumab.* Clin Rheumatol, 2007. **26**(5): p. 787-8.
96. Youdim, A., et al., *A pilot study of adalimumab in infliximab-allergic patients.* Inflamm Bowel Dis, 2004. **10**(4): p. 333-8.
97. Demirel, F., et al., *Desensitization to Adalimumab: An Example of Repeated Desensitization to a Biological Agent.* Drug Saf Case Rep, 2015. **2**(1): p. 7.
98. Fomin, I., et al., *Vaccination against influenza in rheumatoid arthritis: the effect of disease modifying drugs, including TNF alpha blockers.* Ann Rheum Dis, 2006. **65**(2): p. 191-4.
99. van Assen, S., et al., *EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases.* Ann Rheum Dis, 2011. **70**(3): p. 414-22.
100. Heijstek, M.W., et al., *EULAR recommendations for vaccination in paediatric patients with rheumatic diseases.* Ann Rheum Dis, 2011. **70**(10): p. 1704-12.
101. Rosh, J.R., et al., *Retrospective Evaluation of the Safety and Effect of Adalimumab Therapy (RESEAT) in pediatric Crohn's disease.* Am J Gastroenterol, 2009. **104**(12): p. 3042-9.
102. Hyams, J.S., et al., *Safety and efficacy of adalimumab for moderate to severe Crohn's disease in children.* Gastroenterology, 2012. **143**(2): p. 365-74.e2.
103. Malik, S., et al., *The effects of anti-TNF-alpha treatment with adalimumab on growth in children with Crohn's disease (CD).* J Crohns Colitis, 2012. **6**(3): p. 337-44.
104. Schnitzler, F., et al., *Outcome of pregnancy in women with inflammatory bowel disease treated with antitumor necrosis factor therapy.* Inflamm Bowel Dis, 2011. **17**(9): p. 1846-54.
105. Nguyen, G.C., et al., *The Toronto Consensus Statements for the Management of Inflammatory Bowel Disease in Pregnancy.* Gastroenterology, 2016. **150**(3): p. 734-757.e1.
106. Gotestam Skorpen, C., et al., *The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation.* Ann Rheum Dis, 2016. **75**(5): p. 795-810.
107. Pasut, G., *Pegylation of biological molecules and potential benefits: pharmacological properties of certolizumab pegol.* BioDrugs, 2014. **28 Suppl 1**: p. S15-23.

108. Gallitano, S.M., et al., *Use of tumor necrosis factor (TNF) inhibitors in patients with HIV/AIDS.* J Am Acad Dermatol, 2016. **74**(5): p. 974-80.
109. Sumida, K., et al., *Adalimumab treatment in patients with rheumatoid arthritis with renal insufficiency.* Arthritis Care Res (Hoboken), 2013. **65**(3): p. 471-5.
110. Malaviya, A.N., *Landmark papers on the discovery of methotrexate for the treatment of rheumatoid arthritis and other systemic inflammatory rheumatic diseases: a fascinating story.* Int J Rheum Dis, 2016. **19**(9): p. 844-51.