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A retrospective study of patients with biologics treatment at Groote Schuur and Red Cross Children's War Memorial Hospitals

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Declaration

This research reported is based on independent work performed by the candidate, Dr Mohammed Ahmed, and neither the whole work nor any part of it has been, is being, or is to be submitted for another degree to any other university. This work has not been reported or published *prior to registration* for the abovementioned degree.

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Date: …02/04/2020

Abstract

Introduction. The high cost and concern of adverse events, particularly infections, limit the use of biologic disease-modifying anti-rheumatic (bDMARD) therapies. We undertook this retrospective study to document their use for immune-mediated diseases (IMDs) and explore the efficacy, safety, adherence and screening practices prior to initiating bDMARDs in a tertiary referral hospital.

Methods. A folder review of all adult and paediatric patients treated for IMDs with bDMARDs at Groote Schuur and Red Cross Hospitals between January 2013 and December 2019. Clinico-demographic particulars, details of bDMARD therapy, and adverse events were collated. Changes in disease activity were measured by disease-specific tools at 6, 12, 24-months and at the last available visit, and patient adherence to bDMARDs was explored by folder and pharmacy record review.

Results. We studied 151 folders, with 182 bDMARDs uses (29 patients used more than 1 bDMARD). Patients were from rheumatology (n= 38: 13 rheumatoid arthritis; 10 spondyloarthritis, 5 Systemic Lupus Erythematosus (SLE) , 5 inflammatory myositis and 5 other conditions); gastroenterology (n=31; 26 Crohn`s and 5 Ulcerative Colitis), dermatology (n=9; psoriasis), neurology (n=4, ophthalmology (n= 25; 6 scleritis, 18 uveitis, 1 optic neuritis), and paediatrics (n= 45, 26 juvenile idiopathic arthritis , 12 SLE, 7 other conditions). The bDMARDs used were TNF inhibitors (112), rituximab (55), tocilizumab (10), anakinra (3), abatacept (1), and tofacitinib (1).

The vast majority of patients had an excellent response and were in low disease activity or remission at their last available visit. Adverse events included severe infection (4), tuberculosis (TB) (2), mild infection (4), severe allergic reaction (3), mild skin reaction (14), elevated liver enzymes (2), and worsening interstitial lung disease ILD (1). bDMARD Therapy was discontinued in 18 patients, most commonly due to adverse reaction (9), lack of response (3), poor adherence (2), or remission (1). bDMARD Therapy was changed to alternative therapy in 29 patients, most commonly because of poor response (14), or adverse effects (9) or poor adherence (3). Poor adherence or patients lost to follow-up was noted in 18/182 (9.9%). Complete latent TB infection screening with chest x-ray and TB skin test was performed in only 55 (36.4 %) but INH prophylaxis was given to 51/88 (57.9%) of patients prescribed TNFi therapy. Hepatitis B screening performed in 93 (61.6 %) patients, but most patients (72.2 %) were not tested for Hepatitis B core ab. Hepatitis C screening was performed in 81 (53.6 %) patients. Only 88 (58.3%) patients had a recent HIV test. The majority (17.2%) received the influenza vaccine, but only 24 (15.8 %) received pneumococcal vaccination.

Discussion and Conclusion. bDMARD therapy was an effective treatment, and the most common adverse effect was infection (7.2%), with 2 TB infections. Vaccination and screening for TB, viral hepatitis and HIV was suboptimal. Of concern, poor adherence to bDMARDs was frequently encountered.

Key points

bDMARDs are effective treatment

The most common adverse effect was the infection

Screening before starting bDMARDs is important

Vaccination important before starting bDMARDs

Key words

EULAR, BDMARDs, Adherence, Efficacy, Adverse event, vaccination

Chapter 1: The literature review

Background:

Numerous biologic disease-modifying anti-rheumatic drugs (bDMARDs) have been developed over the last two decades, targeting inflammatory cytokines, cytokine receptors or cells within the synovium and immune system. These therapies have dramatically improved outcomes in patients with immune-mediated diseases (IMDs) and are indicated in patients with a poor response to conventional therapy. Recommendations for their use have been published by international and local South African associations including the European League Against Rheumatism (EULAR) and by the South African Rheumatism and Arthritis Association (SARAA)(1,2).

Nine bDMARDs are currently registered and available in SA with good efficacy and safety profile. These include tumour necrosis factor inhibitors (TNFi) which are Infliximab (IFX), Etanercept (ETN), Adalimumab (ADA), Golimumab (GOL); and the non-TNFi, which are Abatacept (ABT), Rituximab (RTX), Tocilizumab (TCZ), Ustekinumab (UTK) **and** Secukinumab (SCK)(3)**.**

The management of any IMDs requires a multiple disciplinary team, shared decision between patients and physician, holistic consideration of the disease and its therapy's medical and social costs. Below we briefly describe each IMD, the tools used for the measurement of disease activity, and the indication and specific bDMARDs that are useful. Tables 1 -3 show summaries of bDMARDs and each disease-specific measurement.

Rheumatoid Arthritis:

Rheumatoid Arthritis (RA) is a polyarticular inflammatory disease with the potential to cause significant disability from joint inflammation and progressive joint destruction(4). Disease activity is measured by the Clinical Disease Activity Index (CDAI), comprising the number of swollen and tender joints, and patient self and physician global assessments(5). The Health Assessment Questionnaire Disability Index (HAQ-DI) measures functional disability (6).

In refractory disease, bDMARDs control inflammation, prevent joint damage and improve functional disability(2). Against this background, SARAA recommends the use of bDMARD for RA in patients who have failed a 6 month trial of at least three conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), including Methotrexate (MTX), Sulphasalazine

(SSZ) and Leflunomide(2). EULAR also considers bDMARD in treatment for RA if treatment to target is not achieved with first csDMARDs in the presence of poor prognostic factors (persistent moderate or high disease activity despite csDMARDs, high acute phase reactant, high swollen joint count, presence of early erosions, presence of rheumatoid factors (RF) and anti-citrullinated peptide antibody (ACPA) especially in high level, and failure of two or more csDMARDs) (1).

Psoriatic and Psoriatic Arthritis:

Psoriasis (PsO) is a chronic skin disorder that affects 2.2% of the population in the united states, characterized by thick, inflamed red patches often covered with silvery scales on the skin(7). Topical agents are the first line but systemic therapy with csDMARDs must be considered for severe disease, and patients failing to respond to csDMARDs require bDMARDs (8,9). EULAR recommends bDMARDs for the management of moderate to severe PsO not responding to other systemic therapies (10). In PsO, disease activity is assessed by body surface area (BSA) and Psoriasis Area and Severity Index (PASI). A BSA >10% signifies moderate to severe disease activity, and a PASI score of 12 is a minimum for entry into many clinical trials (11).

Psoriasis can be associated with arthritis termed psoriatic arthritis (PsA), which can lead to joint damage, functional impairment and increased mortality(12). Disease activity scores include the Psoriatic Arthritis Disease Activity Score (PASDAS), and Composite Psoriatic activity Disease Index (CPADI), but the CDAI used in RA is also frequently used(13). The treatment of active PsA includes early csDMARDs. If the patient is unresponsive to at least one csDMARD, bDMARDs should be considered. These include TNFi, interleukin-17 (IL-17) or interleukin-12/23 (IL-12/23) inhibitors(14). Studies have shown that treatment of psoriatic arthritis with TNFi (ETN, ADA, or IFX) is highly effective with significant improvement in disease activity, functional status, and skin scores(15).

Spondyloarthritis:

Seronegative spondyloarthropathies (SpA) are a group of inflammatory rheumatic diseases with axial and peripheral arthritis, enthesitis, extra-articular manifestations and HLA- B27 association(16). The untreated disease has a negative impact on patient life, fatigue,

depression, sleep problems, and sexual function (17). The Ankylosing Spondylitis Disease Activity Score (ASDAS-CRP) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) are a reliable measurement of disease activity, response to treatment and can be used in daily clinical practice(18). The first-line pharmacological treatment for axial SpA is non-steroidal anti-inflammatory drugs (NSAIDs). For persistent high disease activity despite two different NSAIDs, bDMARDs should be considered - including TNFi or IL- 17 inhibitors(19). SARAA recommends the use of TNFi in patients with persistently elevated BASDAI (≥4) despite 2 NSAIDs(3).In clinical trials of patients with active SpA, treatment with TNFI has shown improvement in function and disease activity, together with reduced radiographic progression(20–22).

Systemic lupus erythematosus:

The systemic lupus erythematosus (SLE) is a chronic IMD that can affect any organ and system of the body with a wide range of complications and significant morbidity and mortality. The most commonly used tools to assess disease activity in lupus are the SLE Disease Activity Index (SLEDAI and the British Isles Lupus Assessment Group (BILAG)(23).

Antimalarial treatment, such as chloroquine, is recommended for all patients with SLE unless contraindicated. Early and prompt initiation of immunosuppressive therapy expedites tapering of glucocorticoids. In refractory organ-threatening disease, and particularly in haematological, neurological and renal manifestations, RTX should be considered(24).

In a systematic review of 188 patients treated with RTX, 171 of the 188 patients showed significant improvement in one or more of the systemic SLE manifestations(25). Rituximab is useful in the treatment of haematological disease, refractory nephritis, and neuropsychiatric systemic lupus erythematosus (NPSLE)(26).

Juvenile Idiopathic Arthritis:

Juvenile Idiopathic Arthritis (JIA) is a chronic arthritis of childhood and is the most common cause of musculoskeletal disability in children(27). This disease is divided into several subgroups including systemic JIA, seronegative polyarticular JIA, seropositive polyarticular JIA, oligoarticular JIA, enthesitis-related arthritis and juvenile psoriatic arthritis(28,29). Untreated disease can lead to persistent inflammation which results in muscle atrophy,

flexion contraction and leg length inequality(30). There is no single measure that can reliably capture overall disease activity in all JIA phenotypes. Composite diseases activity scores including Juvenile Arthritis Disease Activity Score (JADAS) with multiple versions, the Juvenile Arthritis Parent Assessment Index (JAPAI), the Juvenile Arthritis Child Assessment Index (JACAI), the Juvenile Arthritis Multidimensional Assessment Report (JAMAR) and the Juvenile Spondyloarthritis Disease Activity Index (JSpADA) are some of composite disease activity indices used for children and adolescents in JIA(31). For JIA with inadequate response to csDMARDs, bDMARDs including TNFi, anakinra, RTX, ABT and TCZ are indicated(32,33). bDMARDs in patients with JIA may lead to remission, improved quality of life, with normal growth and good long term functional outcome(27,32–34).

Inflammatory Bowel Disease:

Inflammatory Bowel Disease (IBD) encompasses Crohn's Disease (CD), characterized by transmural inflammation affecting any part of the gastrointestinal tract, and Ulcerative Colitis (UC) which causes diffuse mucosal inflammation confined to the colon(35). Serious complication includes a fistula, abdominal abscess, toxic colitis, pouchitis and primary sclerosing cholangitis(36). Disease activity in IBD is measured using clinical parameters, like a daily bowel movement, presence of bloody diarrhoea and laboratory measures like ESR, CRP and Hb(37). In Crohn's disease, the CDAI and Van Hees index(VHI) is used, together with histological and endoscopic indices for mucosal monitoring(38). For ulcerative colitis, it is essential to measure the extent of inflammation by endoscopy or x-ray examination of the bowel(38). Monoclonal TNFi such as IFX has been approved for the treatment of inflammatory and fistulating CD. Others TNFi have emerged for IBD, including certolizumab, GOL and ADA. (39). A Cochrane meta-analysis, and open-label extension follow-up and cohort studies confirm that ADA, IFX, and certolizumab have successfully induced and maintained remission in Crohn's disease(39,40). In addition, the combination of IFX and azathioprine promotes mucosal healing and induces steroid-free remission better than azathioprine or IFX alone(40). In the last two decades in SA, bDMARDs have shown impressive results(41).

Immune-mediated myositis:

Idiopathic inflammatory myopathy (IMM)s are characterized by an inflammatory infiltrate in

the muscle and can affect other organs, particularly the lungs(42). IMMs are classified into dermatomyositis (DM), polymyositis (PM) and inclusion body myositis (IBM)(43,44). Treatment of IIMs include glucocorticoids combined with immunosuppressants(45). RTX and ABT are promising treatments for IIMs and for treating immune-mediated ILD(46–50). The core set measures (CSM) and conjoint-analysis survey are used as response criteria in IMM(47).

Juvenile dermatomyositis

Juvenile dermatomyositis (JDM) is a chronic autoimmune disease characterised by symmetrical proximal muscle weakness and skin involvement(51). The standard treatment includes the combination of a high dose of intravenous or oral Glucocorticoids, and MTX(51). The Single Hub and Access point for pediatric Rheumatology in Europe (SHARE) initiative recommendation for the treatment of refractory JDM includes adding Intra Venous Immuno-Globulins (IVIG) or changing MTX to Cyclosporine A, Mycophenolate Mofetil (MMF), or bDMARDs which includes RTX, IFX or ADA(52). Regular reviews include assessment of skin disease, muscle strength, major organs involvement, and patient/parent report outcome measures(52). Measures of disease activity include patient/parent global health score, physician global, patient pain score and childhood myositis assessment score (CMAS), which is the most commonly used assessment tool(53).

Uveitis and Scleritis:

Uveitis is inflammation of the uveal tract including the iris, ciliary body and choroid, and maybe a part of systemic diseases such as SpA, IBD, JIA, Bechet's and Sarcoidosis. Uveitis is the most common ophthalmological finding in rheumatology and clinical immunology and can lead to amblyopia, significant morbidity, and blindness(54). Off-label use of bDMARDs, particularly monoclonal TNFi are very effective in refractory uveitis and retinal vasculitis and improve quality of life(55–57). The Standardization of Uveitis Nomenclature (SUN) criteria is used to measure disease activity in uveitis however, it only takes into account inflammation in the anterior chamber and vitreous haze. The Uveitis Disease Activity Index (UVEDAI) and visual acuity (VA) are used to assess disease activity(58,59).

Scleritis is inflammation of the sclera can be classified to anterior and posterior or necrotizing

and non-necrotizing(60). bDMARDs are indicated for scleritis that poorly responds to corticosteroids and/or to immunosuppressive treatment. Monoclonal TNFi including IFX and ADA are superior to ETN for the treatment of refractory scleritis. In scleritis associated with vasculitis, RTX is the best option(61). Ophthalmological clinical evaluation is used to assess scleritis and the response to bDMARDs(62).

ANCA-associated vasculitis and Bechet's disease*:*

Vasculitis is the inflammation of the vessels wall with or without necrosis. The Birmingham Vasculitis Activity Score (BVAS), The Birmingham Vasculitis Activity Index (BVAI) for Granulomatosis with polyangiitis (GPA) (BVAI/GPA), a Physician Global Assessment (PGA), the Disease Extent Index,(DEI), and the Five-Factor Score(FFS) are globally accepted as vasculitis disease activity measurement tools(63). RTX or cyclophosphamide regimens lead to sustained remission in ANCA- associated vasculitis(64,65).

Bechet's disease (BD) is a multisystem disease characterized by oral and genital ulcers, eye involvement (uveitis, retinal vasculitis), neurological involvement (stroke, meningoencephalitis), articular involvement, skin involvement, GIT involvement and vascular involvement(arterial and venous thrombosis, aneurysm)(66). Both TNFi (IFX and ADA) are effective treatments(67). The Behçet's Syndrome Activity Scale (BSAS) and the Behçet's Disease Current Activity Form (BDCAF) were useful measurements to assess disease activity. Of BD(68).

IgG4 sclerosing-related disease:

IgG4 sclerosing-related disease (IgG4-RD) is multi-organ IMD links that mimic inflammatory conditions, infection and malignancy. The pathological features are lymphoplasmacytic infiltration, fibrosis and obliterative phlebitis. Untreated disease can lead to organ damage with extensive fibrosis and death(69). Serial treatment with RTX leads to better control of the disease activity and a decrease in serum IgG4 concentration(70). The IgG4-RD Responder Index (RI) is a reliable and valid disease activity assessment that can be used to assess response to treatment(71).

Safety of biologics:

Although bDMARDs are highly effective in treating IMD's, important safety concern has emerged. These include administration reactions, infection, malignancy, demyelinating disease, congestive heart failure and hyperlipidemia(72).

Infections

Biologic therapy increases the risk of both mild and serious infections(2,73). In sub-Saharan Africa, there is a heavy burden of infectious diseases, including tuberculosis (TB), HIV, hepatitis B and C virus and these need careful monitoring in patients using any biologic treatment(3).

Tuberculosis

All RA patients in SA are at increase the risk of TB, and this risk is increased with age (≥60 years), previous TB infection, low socioeconomic status and high-risk occupation or dwelling, for example, health worker, homeless and prisoner-staff(2). Most importantly, the background risk of TB influences the risk of reactivation of latent TB infection (LTBI) or reinfection with TB(2). bDMARDs have an increased the risk of TB, however, the risk of TB between bDMARDs varies significantly with the highest risk with TNFi particularly ADA and IFX, and the lower risk of TB associated with newer TNFi and other bDMARDs(74). In countries with a high risk of TB, non-TNFi should be considered the first-line bDMARD for RA, because of the risk of TB associated with TNFI(75). Because of TNF-α 's role in maintaining granuloma integrity, TNF inhibition is associated with reactivation of latent TB, in experimental models and in human patients(76). The TB risk is 3-4 times higher in monoclonal TNFi than soluble TNFi (ETN)(77). Similarly, interleukin-1 (IL-1) is essential for host resistance to mycobacterium TB, and IL-1 inhibitors are associated with an increased risk of TB infection and reactivation(76). Interleukin-6 (IL-6) is associated with differentiation of IL-17 and interleukin-22 (IL-22) which possesses anti-mycobacterial properties, and IL-6 deficiency associated with TB death in mice(76). The TB risk of a patient treated with RTX or ABT was negligible, and the TB screen has been suggested to be unnecessary(76). However, a recent retrospective review of the SA bDMARD registry show occurrences of TB in all bDMARD users(78). From the available evidence and SCK appear safe in a patient with latent TB(76).

Screening for active TB with a chest X-ray (CXR) together with screening for LTBI with either a

tuberculin skin test (TST) or Interferon Gamma Release Assay (IGRA) is mandatory before commencing bDMARD. Both tests only measure the magnitude of effectors' memory T cells response to previous or recent exposure, and neither of these tests distinguishes LTBI from active TB. Patients with a positive test are more likely to develop TB within the next two years(2,79). Screening LTBI and offering isoniazid (INH) prophylaxis for positive cases has resulted in a marked reduction in TB risk and is now part of international and local recommendations before commencing biologic therapy(2,80). Recommendations are that patients complete at least 4 weeks of INH therapy prior to starting a TNFi. However, studies have shown that adherence to these recommendations is poor(81,82). Many state-sector rheumatology services in SA including GSH, have taken the decision to offer continuous INH prophylaxis for an extended period for the duration of TNFi therapy to all patients' prescribed TNFi therapy, regardless of LTB screening results.

Viral Hepatitis

The bDMARDs infer a risk of reactivation of Hepatitis B and C viruses, and RTX, in particular, has a greater risk of hepatitis B virus reactivation(83). Screening with Hepatitis B surface antigen (HBsAg), anti-hepatitis B surface (anti-HBs), anti-hepatitis B core total (HBcab), Hepatitis C virus antibodies (HCV ab) should be done in all patients before commencing biologic therapies(84,85).

Other infections

All bDMARDs infer an increase of serious and mild infections. Patients and health care workers need to be aware of this risk and to assess and treat unwell patients rapidly with a high index of suspicion for infection. In particular, tofacitinib increased the risk of herpes zoster infection(86). The most common adverse effect of anakinra was pneumonia and gastroenteritis(87). HIV-infected individuals have not been included in randomized control trials of bDMARDs because of increased risk of infection so the use of bDMARD therapy in HIV positive patients is limited to case series and case reports and needs further study(88).

Vaccination:

Before commencing bDMARDs, patients need immunization for influenza, pneumococcal, human papillomavirus and hepatitis B virus. Live vaccines including herpes zoster and yellow

fever are not recommended(2,89).

Other side effects

An uncommon but serious adverse effect of TNFi includes uveitis, drug-induced SLE and demyelination(Table 4)(90). The most common side effects of TCZ include serious infection, elevated liver enzymes, and neutropenia(91). The most common adverse effect of RTX is infusion reactions, neutropenia, with concerns of progressive multifocal leukoencephalopathy, and agammaglobulinemia in long-term use(79,92). Treatment with ABT is associated with lower risks of infection, autoimmune events, and infusion reactions(93). Adverse effects of tofacitinib include gastrointestinal perforation, increased risk of malignancy and major cardiovascular events(86). The most frequent adverse effects of anakinra are headache, arthralgia and injection site reactions occurred mainly during the first-month treatment(87).

Pregnancy

Studies have shown that TNFi is safe throughout pregnancy and are not associated with an increase in maternal or foetal adverse events except for the risk of neonatal TB following Bacillus Calmette Guerin (BCG) vaccination, which should be deferred(94). Tofacitinib should be discontinued at least 6 weeks before planned pregnancy and during breastfeeding(95). Anakinra can be used in pregnancy in the absence of alternative treatments(96). There is insufficient data on the safety of RTX, belimumab, UTK SCK, and TCZ and these should be avoided during pregnancy and breastfeeding(96).

Adherence and support:

Adherence to bDMARDs is less than expected. In a recent study of RA patients treated with bDMARDs in five different European countries, 56.3% of patients missed a dose over 6 months. The reasons for noncompliance were feeling better and didn't need it, thinking the therapy was not helping, sickness, surgery or infection(97). Similarly, adherence in PSO is low with a high discontinuation rate(98).

Adverse effects, particularly infection and TB, together with the high cost of these therapies, hampers their widespread use and makes evaluation of efficacy and safety practices associated with their use vital(3). We undertook this retrospective review of all patients

treated with bDMARDs for IMD in the last 7 years at Groote Schuur and Red Cross Hospitals to measure the efficacy, safety, and adherence of patients to biologic treatment. This will promote a deeper understanding of the use of these therapies in sub-Saharan, Africa and will allow better planning of future health care services.

Table-1 Biologic DMARDs available in EULAR - mechanism of action of and indications

Biologic Drug	Mechanism of action	Registered indications	Off-label indications
Infliximab	Monoclonal antibody against TNF ά (Murine and human antibody)	AS, CD, JIA, PsA, RA, UC Hidradenitis suppurativa Plaque psoriasis Uveitis (except Etanercept)	Graft-vs-host disease Pustular psoriasis Pyoderma gangrenosum
Adalimumab	Fully Human Monoclonal antibody against TNF-ά		
Golimumab	Fully human Monoclonal antibody against TNF ά		
Etanercept	Fusion protein fused with FC portion of human IgG1 and block against TNF-ά		
Abatacept	Soluble fully human Fusion protein inhibitor T-cell co-stimulation	RA, JIA, PsA	
Rituximab	Chimeric Mouse/human monoclonal antibody against CD 20+ B cells	RA, GPA, MPA Non-IMD indications - NHL, CLL	Inflammatory myopathies Pemphigus Vulgaris, SLE
Tocilizumab	Humanized monoclonal antibody targeting IL 6 receptor	RA, sJIA, NMO, GCA	Crohn's disease, SLE. PMR
Ustekinumab	IL-12/23 monoclonal antibody	PSO, PsA, CD	UC
Secukinumab	IL-17 inhibitor	PSO, PsA, AS	
Tofacitinib	Janus kinase (JAK) inhibitor	RA, UC	

AS: Ankylosing Spondyloarthritis; CD: Crohn's Disease: CLL: Chronic Lymphocytic Leukemia; GCA: Giant Cell Arteritis; IBD: inflammatory bowel disease; JIA: Juvenile Idiopathic Arthritis; MPA: Microscopic Polyangiitis; NHL: Non-Hodgkin Lymphoma; NMO: Neuromyelitis Optica; PSO: psoriasis; PsA: Psoriatic Arthritis; PMR: Polymyalgia Rheumatica; RA: rheumatoid arthritis; sJIA: Systemic Juvenile Idiopathic Arthritis; SLE: Systemic Lupus Erythematosus; UC: Ulcerative Colitis; GPA: Granulomatous with polyangiitis.

Table 2 Dose and administrative route of Biologic DMARDs currently available in EULAR

Biologics	Half-life(days)	Route	Dose (adult patients)	Dose (Pediatric patients)	frequency
Infliximab	8-10	IV	3mg/kg	3mg/kg	8 weeks
Adalimumab	10-20	S/C	40mg.	20 mg in children < 30kg	2 weeks
Etanercept	4	S/C	50mg	.8mg/kg	weekly
Golimumab		S/C	50mg		Monthly
Rituximab	19-22	IV	500-1000mg,	750mg/m2, maximum dose 1g	2 doses 2 weeks apart every 6months or at disease flare
Tocilizumab	13	IV	8mg/kg	8mg/kg	2 weeks
Abatacept	8-25	IV	500mg, 750mg, or 1000mg	-If < 75 kg: 10 mg/kg IV -If 75 kg to 100 kg: 750 mg IV -If > 100 kg: 1000 mg IV -Maximum dose: 1000 mg	4 weeks
Ustekinumab	20-39	S/C	45mg if weight ≤ 100 kg 90mg if weight ≥ 100 kg		12 weeks
Secukinumab	17-41	S/C	150mg		4 weeks

Abbreviations:

IV: Intravenous; S/C: Subcutaneous; M2: meter squire.

Table 3: Disease-specific outcome measures

	Disease	Disease activity measurement
RA		CDAI, C- Reactive Protein (CRP)
AS		BASDAI, BASFAI, CRP
Psoriasis		PASI, BSA%, Clinical features (C/F), EIS
PsA		CPADI, CDAI
IBD		C/F, colonoscopy, CDAI
IgG4-RD		C/F, IgG4-RD(RI)
JIA		cJADAS-10, JAMAR, JACAI, JSpADA,
SLE	AIHA	haemolysis
	Pulmonary vasculitis, shrinking lung syndrome	Lung function tests (including DLCO)
	nephritis	Remission criteria
	Arthritis	CDAI
	thrombocytopenia	Platelet count
	Neurolupus	C/F
AOSD		CDAI, CRP
IMMs		CK, CSM, C/F, CMAS for JDM
Vasculitis-GPA		C/F, BVAI/GPA
Behçet's disease		BSAS, BDCAF
PAN		C/F, BVAS
MPA-ILD		Lung function tests C/F
MPA		UPCR, Cr
Uveitis		VA, C/F, IOP
Myasthenia Gravis		MG composite score, C/F
Multiple sclerosis		EDSS, C/F
NMO		C/F
CRMO		C/F
Sweet syndrome		C/F
Autoinflammatory syndrome		C/F

Abbreviations: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFAI: Bath Ankylosing

Spondylitis Function Activity Index; BDCAF: Behçet's Disease Current Activity Form; BSAS: Behçet's Syndrome Activity Scale; BVAI/GPA: Birmingham Vasculitis Activity Index for Granulomatosis with polyangiitis; BVAS: Birmingham Vasculitis Activity Score; CDAI: Clinical Disease Activity Index; CRP: C Reactive Protein; C/F: Clinical Features; CK: Creatinine Kinase; CMAS: Childhood Myositis Assessment Score; CSM: Core Set Measures; cJADAS-10: clinical Juvenile Arthritis Disease Activity Score-10 joints; IgG4-RD(RI): IgG4-RD Responder Index; JACAI: Juvenile Arthritis Child Assessment Index; JSpADA: Juvenile Spondyloarthritis Disease Activity Index; PASI: Psoriatic Area Severity Index; BSA%: Body Surface Area%; EIS: Erythema, Induration, Scaling; VA: Visual Acuity; IOP: Intra Ocular Pressure; NMO: Neuro Myelitis Optica; CRMO: Chronic Recurrent Multifocal Osteomyelitis.

Table 4: Adverse effects of Biologic DMARDS and preventative measures

problem	bDMARD risk	Other risks	prevention
Tuberculosis	monoclonal TNFi >. soluble TNFi > non-TNFi. (TCZ (very low risk), tofacitinib)	….	Screening for LTB, INH prophylaxis
Hepatitis B Virus	RTX TNFi Other biologic drugs	GC, Anthracycline derivative's (Doxorubicin)	Screening for HBV S Ag, HBV Core Ab before immunosuppression. Prophylaxis of patient with HBc Ab +ve.
Hepatitis C Virus	There is no risk of reactivation with immunosuppressive drugs.		HCV Ab, if positive HCV RNA should be checked. Contraindication in liver dysfunction classified as Child–Pugh class B and higher
Urinary Tract Infections	ABT		
URTI and LRTI (pneumococcal, Influenza, PCP)	TNFi, ABT, TCZ, UTK, SCK, tofacitinib, anakinra	HIV, GCs.	Vaccination, prophylaxis treatment for PCP
Herpesvirus (EBV, CMV, HSV, VVZ)	VZV (TNFi) HZV Tofacitinib	EBV (Thiopurine, Aza) CMV (steroid severe refractory IBD) immunosuppression	Check VZ Ab before commencing immunosuppression. In the presence of negative tests, vaccination should be offered a least 4 weeks before immunosuppression
Neutropenia	TCZ	csDMARDs	Full Blood Count (FBC)
Demyelination	TNFi	Checkpoint inhibitor	with most cases having a partial or complete response to steroids and discontinuation of the offending agent.
Progressive multifocal leukoencephalopathy	RTX Natalizumab		Watch for neurological symptoms if present considers MRI and virus antibody.
transaminitis	TCZ ABT		Follow up by liver function test
Dyslipidemia	TCZ		Lipid profile
GIT perforation	TCZ		
Infusion reaction	TNFi, RTX, ABT, TCZ, UTK, SCK		Sow infusion, and watch for rash and itching, and breathing difficulties

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Chapter 2

Submission ready manuscript

TITLE PAGE

Title: Efficacy, adverse events and adherence amongst patients using Biologic therapies at Groote Schuur and Red Cross Hospitals.

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Abstract

Introduction. The high cost and concern of adverse events, particularly infections, limit the use of biologic disease-modifying anti-Rheumatic drugs (bDMARD) in South Africa. We undertook this retrospective study to document their use for immune-mediated diseases (IMDs) and explore the efficacy, safety, adherence and screening practices prior to initiating to bDMARDs in a tertiary referral hospital.

Methods. A folder review of all adult and paediatric patients treated for IMDs with bDMARDs at Groote Schuur and Red Cross Hospitals between 01/2013 and 12/2019. Clinico-demographic particulars, details of bDMARD therapy, and adverse events were collated. Changes in disease activity were measured by disease-specific tools at 6, 12, 24-months and at the last available visit, and patient adherence to bDMARDs was explored by folder and pharmacy record review.

Results. We studied 151 folders, with 182 bDMARDs uses (29 patients used more than 1 bDMARD). Patients were from rheumatology (38) gastroenterology (31); dermatology (9), neurology (4), ophthalmology (25;), and paediatrics (45). The bDMARDs used were tumour necrosis factor inhibitors (TNFi) (112), rituximab (55), tocilizumab (10), anakinra (3), abatacept (1), and tofacitinib (1).

The vast majority of patients had an excellent response and were in low disease activity or remission at their last available visit. Adverse events included severe infection (4), tuberculosis (TB) (2), mild infection (4), severe allergic reaction (3), mild skin reaction (14), elevated liver enzymes (2), and worsening interstitial lung disease (ILD) (1). bDMARD therapy was discontinued in 18 patients, most commonly due to adverse reaction (9), lack of response (3), poor adherence (2), or remission (1). bDMARD Therapy was changed to alternative therapy in 29 patients, most commonly because of poor response (14), or adverse effects (9) or poor adherence (3). Poor adherence or patients lost to follow-up was noted in 18/182 (9.9%). Complete latent TB infection screening with chest x-ray and TB skin test was performed in only 55 (36.4 %) but isoniazid prophylaxis was given to 51/88 (57.9%) of patients prescribed TNFi therapy. Hepatitis B virus (HBV) screening performed in 93 (61.6 %) patients, but most patients (72.2 %) were not tested for HBV core antibody. Hepatitis C virus screening was performed in 81 (53.6 %) patients. Only 88 (58.3%) patients had a recent human immune virus (HIV) test. The majority (17.2%) received the influenza vaccine, but only 24 (15.8 %) received pneumococcal vaccination.

Discussion and Conclusion. bDMARD therapy was an effective treatment, and the most common adverse effect was infection (7.2%), with 2 TB infections. Vaccination and screening for TB, viral hepatitis and HIV was suboptimal. Of concern, poor adherence to bDMARDs was frequently encountered.

Key points

The most common adverse effects of bDMARDs are mild infusion reactions and infection.

Screening and vaccination before starting bDMARDs is important and poorly adhered to

Keywords

South Africa, bDMARDs, Efficacy, Adverse event, vaccination

Introduction:

Biologic disease-modifying anti-rheumatic drugs (bDMARDs) have dramatically improved outcome in patients with severe immune-mediated diseases (IMD). They are indicated in autoimmune diseases that have shown a poor response to conventional therapy, and recommendations for their use have been published by international and national bodies representing various subspecialties (1,2).

All bDMARDs increases the risk of serious infection (2–5). In sub-Saharan Africa, there is a heavy background burden of infectious diseases, including tuberculosis (TB), human immune virus (HIV), and hepatitis B (HBV) and hepatitis C virus (HCV) and these need careful monitoring in patients using any bDMARD treatment (3,6). The concern of serious infection, together with the high cost of these therapies, hampers the widespread use of bDMARDs in resource-constrained settings and evaluates efficacy and safety practices associated with their use vital. In the South African (SA) state- sector, resource constraints mean that very few state-sector patients are offered bDMARDs(3). Each clinical division needs to motivate for a bDMARD to the pharmacy therapeutics committee on a named patient basis. Alternatively, patient self-funding, medical insurance schemes, or clinical trials are ways of accessing these therapies. In SA, there are considerable variations in access to bDMARDs between hospitals and provinces.

We undertook this study to assess the number of patients, indications for, and specific bDMARD therapies used, in addition to monitoring efficacy, adverse events and screening practices. We believe an understanding of these metrics will improve our current use and future planning of therapies for refractory patients.

Patients and Methods

This retrospective study includes all patients treated with bDMARDs for IMD at a tertiary referral hospital. We included any patient given bDMARDs (minimum one dose) between January 2013 and December 2019 and excluded patients treated for haematological malignancy. To ensure all patients using bDMARDs were included, lists were obtained from each clinical department, and the hospital pharmacy.

Folders were reviewed, and demographic and clinical details including the IMD details and

disease duration, use of immunosuppressant before bDMARDs, and screening procedures were documented. Disease activity, measured by accepted disease-specific tools, were documented at baseline, 6-, 12- and 24- months, and at the last available encounter, together with adverse events and reason/s for discontinuation of treatment. Besides, patient adherence was assessed by reviewing the pharmacy records of prescriptions filled.

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The Student's t-test was applied to compare continuous variables between independent groups, except where there was non-normal distribution in which case the Wilcoxon rank-sum (Mann Whitney) test was used. A p-value of 0.05 was considered significant. Statistical analyses were done using Statistica 13.5.17software. This study was approved by the University of Cape Town Human Research Ethics Committee.

Results

We reviewed 151 folders, with 182 bDMARDs prescribed (29 patients used more than 1 bDMARD), of which 100 were females and 51 males; 91 were adults and 60 pediatric patients (Table 1). Eleven folders were excluded from the study because they were lost, destroyed or empty. The adult patients were Crohn`s disease (CD) (26), rheumatoid arthritis (RA) (13), spondyloarthritis (SpA) (10), ophthalmology (10), psoriasis (PSO) (9), systemic lupus erythematosus (SLE) (5), ulcerative colitis (UC) (5), idiopathic inflammatory myopathy (IIM) (5), neurology (4), and other diagnoses (4). The pediatric patients were juvenile idiopathic arthritis (JIA) (26), ophthalmology (15), SLE (12), vasculitis (3) and other diagnoses (4). The vast majority of bDMARDs were state-funded, with 7 patients paying for their bDMARDs personally or through private medical insurance, and 1 patient enrolled in a clinical trial. Disease duration before starting bDMARD therapy was long (mean (SD) 7.08 (7.21)), and the majority of patients had used numerous immunosuppression before bDMARDs, reflecting the poor access to these expensive therapies.

Disease activity and response to treatment

As expected, the vast majority of patients showed significant improvements in disease activity on bDMARD therapy (Table 2 and 3). Amongst RA and SpA patients, 66.6% achieved low disease activity. Improvements were seen in 88.8% of PSO patients, 80.0% of Inflammatory bowel disease (IBD) patients, 84.6% of JIA patients and all ophthalmology

patients. There were a few patients who showed no improvement – the CD with fissure on TNFi, and the adult-onset still disease (AOSD), polymyositis (PM), juvenile dermatomyositis (JDM) and 2 neurology patients treated with RTX. Most adult and paediatric SLE patients improved except for two patients with nephritis.

Screening practices

We reviewed the screening and vaccination practices prior to bDMARD initiation (Table 4). In terms of TB, 12 (7.9%) patients reported previous TB, chest radiographs (CXR) were abnormal in 5 (3.3 %) patients, normal in 140 (92.7 %) patients and not performed in 6 (4.0%) patients. Screening for latent TB infection (LTBI) with a tuberculin skin test (TST) was positive in 10 (6.6%) patients, negative in 45 (29.8 %), and not done in 96 (63.6%). Of the patients treated with TNFi, only 37/88 (42%) had a TST performed. Of these 12/37 (32.4%) were from rheumatology, 2/37 (5.4%) in dermatology, 12/37 (32.4%), in gastroenterology, 7/37 (18.9%) in JIA, and 4/37 (10.8%) in pediatric ophthalmology. However, the decision was made in some subspecialties to prescribe long-term isoniazid (INH) prophylaxis to all patient on TNFi, thus the TST was not always performed as the results were felt to be irrelevant. Long-term INH prophylaxis was given to 71/151 (47%) bDMARD patients, and to 44/88 (57.9%) of the patients prescribed TNFi therapy. Of these, 21/44 (47.7%) from rheumatology, 13/44 (29.5) ophthalmology, 11/44 (25%) in gastroenterology, and 2/44 (4.5%) in dermatology). Short term INH prophylaxis for 6-months was given to 10/151 (6.6%) bDMARDs patients and to 7/88 (8%) of patients prescribed TNFi therapy.

Screening for HBV surface antigen (HBsAg) was performed in 93 (61.6%) patients, and by division, 33.3% in rheumatology, 29% in gastroenterology, 11.8% in pediatric rheumatology, and under 10% in all other Departments The vast majority of patients (72.2%) had no testing for HBV core antibody (HBcab), and 36 (33 %) of these patients were treated with RTX.

HCV screening was performed in 81 (53.6%) patients. Of these,37% in rheumatology, 23.5% in gastroenterology, 11.1% in pediatric rheumatology and under 10% in other Departments.

HIV testing was performed in 88 patients (58.3%). Three patients were HIV positive and virally suppressed before starting bDMARDs.

In terms of vaccination, few patients received influenza or pneumococcal vaccine (17.2%)and (15.8%) respectively.

Adverse events and discontinuation

Thirty adverse reactions were recorded, and mild skin adverse reactions were the commonest problem, followed by infection (table 5). Two patients had mild infection lead to temporary stopping the bDMARDs, and eight patients had severe infections, necessitating discontinuation of bDMARD in five. These included two patients with TB, the first patient with SpA completed 3 years of etanercept (ETN) with chronic INH prophylaxis and presented with constitutional symptoms and a chest X-ray showing hilar lymphadenopathy. Sputum gene expert and culture were negative, mediastinal lymph node biopsy showed granulomatous inflammation, but Zeil-Nelsen stain was negative. The ETN was discontinued and the patient improved with 6 months of empiric TB therapy. The second patient with RA treated with adalimumab with a negative TST and no INH prophylaxis developed disseminated TB during the first 6 months of bDMARD therapy. Pneumocystis Jiroveci pneumonia (PJP) was diagnosed in an HIV negative RA patient after nearly 4 years of ETN treatment. Varicella was diagnosed in a JIA patient treated to remission with ETN for 3 years.

Eighteen patients (11.9 %) discontinued bDMARDs, with infection 5/18 (27.8%), poor response 3/18 (16.7%), or poor adherence 4/18 (27.8%) being the common reasons for discontinuation. One JIA patient stopped treatment after 9 months of Tocilizumab due to suspected macrophage activating syndrome. One patient became HIV positive during bDMARD treatment, and the bDMARD was stopped given his inactive disease.

HIV positive patients

Of the three HIV positive patients, two had polymyositis (PM), and received RTX after failing numerous immunosuppressive therapies. Both had a mild to moderate clinical and laboratory response to RTX. The third patient with JIA achieved remission with ETN. None of these patients experienced adverse effects and had undetectable viral loads and normal CD4 count throughout treatment.

Switching DMARDs

There were 29/151 (19.2%) patients switching bDMARDs, and two of them switched to more than one bDMARD (tables 6 and 7). The most common reasons for switching bDMARDs was a poor response to bDMARDs or severe reaction. Infection was reported in 3/31 (9.7%).

Adherence

Poor adherence to bDMARDs therapy was observed in 17/151 (9.3 %), and also, four patients were lost to clinic follow-up. Despite our attempts to trace these patients, no details are available. These patients may have relocated or may have died at home.

Discussion

We have described the patients using bDMARD at a tertiary referral hospital and show that the commonest class of bDMARDs prescribed is TNFi (61.5%), followed by rituximab (RTX) (30.2%), with the most common indications including inflammatory arthritis, IBD, PSO and scleritis. Most bDMARDs were state-funded. The vast majority of patients had an excellent response to bDMARDs, which is encouraging, despite the long disease duration and numerous immunosuppressants used before starting bDMARDs.

Validated disease assessment scores were documented in the folders of most patients. A serum C-reactive protein (CRP) was seldom performed in bDMARD patients, and this may be an area for improvement, given that CRP is a useful measure of inflammation, and may also be a marker of TB or other chronic infection(7). The assessment of functional status was very poor, with no regular assessment in either adult or pediatric rheumatology patients. Assessing functional status is vital to assess how symptoms affect patients, and to measure whether therapy is improving the quality of life.

Screening for latent TB is recommended by international and local recommendations before starting bDMARDs (2,5,8–10). Adherence to screening was worryingly poor, given the high prevalence of TB in SA. Although the majority of patients had a CXR, almost a third of patients using bDMARDs had no documented TST. A limited supply of purified protein derivative in the last two years in SA may explain the lack of TST testing. The expense and lack of availability of interferon-gamma release assay in the state-sector limited its use. In a

multicentre retrospective study of Crohn's disease patients using TNFi in Dutch, the adherence to screening for LTBI was 76%(11). INH prophylaxis was only prescribed for 58.0% of patients on TNFi, 52.5%of adults, and 69.0% of pediatric patients, despite the high incidence of TB in SA. Besides, we showed very poor adherence to HBV and HCV testing. Studies from elsewhere have shown that adherence to these recommendations is poor (12,13).

Only 41.7% of patients using bDMARDs in this study had an HIV result available, although SA has one of the highest prevalence of HIV infection in the world. There is currently little literature available regarding the safety of bDMARDs in HIV positive patients (14). Vigilance in knowing the patient's HIV status may guide clinicians' decisions of bDMARD and prophylactic medications will also contribute to the scientific knowledge available.

All bDMARDs therapies modulate the immune response as part of their mechanisms of action, and therefore they may increase the risk of developing infections, particularly in older patients or in patients with concomitant corticosteroids. Some of these infections may be preventable by immunization (15). Before commencing bDMARDs therapy, immunization for influenza, pneumococcal, human papillomavirus and HBV are recommended (3,16–18). In the current study, immunization for influenza and pneumococcus was vaccine suboptimal.

Almost 10% of patients were poorly adherent to their bDMARDs, particularly rheumatology, IBD, and pediatric patients. Reason for poor adherence included a poor understanding of bDMARDs, poor socioeconomic status, adverse effect, and cost. In a recent study of patients treating with bDMARDs in five different European countries, 56.3% of patients missed a dose in the last 6 months. The reasons for noncompliance were feeling better and didn't need it, thinking the therapy was not helping, or sickness, surgery or infection (19). Adherence to bDMARDs therapy in a patient with PSO is low with a high discontinuation rate (20). A prospective study of TNFi in SA showed a third of the patients discontinue TNFi within one year of treatment(21). We recommend a focus on patients' socio-economic backgrounds, with intensive and repeated counselling for all patients taking bDMARDs.

Limitations of this study include the retrospective design, with missing folders, and missing details including function status, and CRP. The other limitation was the lack of specific measurement of activity in some diseases.

In conclusion, bDMARDs in our hospital were effective, and generally safe, with the most common adverse effects being infusion reaction, and infection, with TB occurring in two patients. We note poor adherence to TB and viral hepatitis screening and vaccination before commencing bDMARDs. Also, adherence to bDMARDs was suboptimal. We recommend the preparation of standard operating procedures for all patients using bDMARDs across all disciplines, including details of screening tests before starting bDMARDs, assessment of functional status in patients, and intense patient education and counselling. Further studies are planned to assess the success of these interventions.

Table 1: Details of 151 patients prescribed bDMARDs

CLINICAL DIVISION	DIAGNOSIS	NO OF PTS	AGE AT DIAGNOSIS (YRS, MEAN, (SD)	DISEASE DURATION (YRS. (MEAN, (SD)	NO OF PREVIOUS I/S**	TNFI	RTX	TCZ	OTHER*
RHEUMATOLOGY	RA	13	34.6 (12.6)	9 (10.1)	4	4	9	0	0
N=38	SpA	10	33 (7.1)	8.7 (8)	3	10	0	0	0
	SLE	5	20 (4.2)	5.6 (5.6)	5	0	5	0	0
	AOSD	1	26	5	4	0	1	0	0
	IgG4-RD	1	35	3	1	0	1	0	0
	IIM	5	38.8 (8.5)	8.6	6	0	5	0	0
	PsA	1	33		4	1	0	0	0
	ANCA-Vasculitis	1	22	7	3	0	1	0	0
DERMATOLOGY N=9	PSO	9	38.9 (15.7)	19.3 (9.6)	4	9	0	0	0
GASTROENTEROLOGY	CD	25	24 (10.9)	7.6 (5.8)	5	25	0	1	0
N=31	UC	5	23.6 (18.3)	9.8 (5.3)	4	5	0	0	0
	Skin-CD	1	26	19	2	1	0	0	0
NEUROLOGY	M gravis	1	13	31	3	0	1	0	0
N=4	PM	1	32	10	2	0	1	0	0
	NMO	1	34	3	2	0	1	0	0
	MS	1	24	.2	0	0	1	0	0
OPHTHALMOLOGY	Uveitis	4	21.5 (24.1)	5.4 (4.6)	4	4	0	0	0

N=10	Scleritis	5	36.8 (13.4)	4.8 (3.7)	6	1	4	0	0
	Ulcerative keratitis	1	42 (No SD	1	3	0	1	0	0
PEDIATRIC	JIA	26	7.6 (4.3)	4.6 (5.2)	6	21	3	8	2
RHEUMATOLOGY	SLE	12	9.8 (3.4)	9.8 (3.7)	6	0	12	0	0
N=45	Vasculitis	3	10.6 (1.2)	4 (1.7)	5	0	3	0	0
	Sweet syndrome	1	1	2	1	0	0	0	1
	CRMO	1	8	2	2	1	0	0	0
	Autoinflammatory syndrome	1	10	7.8	3	1	0	0	0
	JDM	1	33	5	4	0	1	0	0
PAEDIATRIC	Uveitis	14	6.2 (2.7)	2.8 (1.8)	4	14	0	0	0
OPHTHALMOLOGY	Optic neuritis	1	9	7	2	0	1	0	0
N=15									

*other – Abatacept, Anakinra

** previous immunosuppressants: Methotrexate, Sulphasalazine, Chloroquine, Leflunomide, Cyclophosphamide, Azathioprine, Mycophenolate Mofetil, Cyclosporin, and Tacrolimus.

Abbreviations: i/s: immunosuppressant**; AOSD:** Adult-Onset Still Diseases**; CD:** Crohn`s disease**; CRMO:** Chronic Recurrent Multifocal Osteomyelitis**; IgG4-RD:** Immunoglobulin 4 Related Diseases**; IIM:** Idiopathic inflammatory myopathy**; JDM:** Juvenile Dermatomyositis**; JIA:** Juvenile Idiopathic Arthritis**; M Gravis:** Myasthenia Gravis**; MS:** Multiple Sclerosis**; PM:** Polymyositis**; NMO:** Neuromyelitis Optica**; PsA:** Psoriatic Arthritis**; PSO:** Psoriasis**; RA:** Rheumatoid Arthritis**; SpA:** Spondyloarthritis**; Skin CD:** Skin Crohn`s disease**; SD:** Standard Deviation**; SLE:** Systemic Lupus Erythematosus**; TCZ:** Tocilizumab**; TNFi:** Tumour Necrosis Factor Inhibitor**; UC:** Ulcerative Colitis**.**

Table 2: Outcomes in adults treated with bDMARDs

Disease		Outcome tool	Baseline (mean, (SD))	6 months (mean, (SD))	12 months (mean, (SD))	p-value*	24-months (mean, (SD))	Last visit No (%) with satisfactory response**
RA n=13		CDAI	60.8 (34.4)	17.0 (14.2)	19.7 (10)	0.01	6.2 (34)	8 (66.6%)
SpA n=10		BASDAI	6,.9 (1.4)	4.5 (2.6)	2.8 (0.2)	<0.0001	2.8 (0)	6 (66.6%)
		BASFAI	9.26 (0.5)	8.4 (1.5)	5.7 (2.0)	0.03		-
PSO n=9		BSA	29.1 (12.5)	9.6 (13.2)	11.3 (12.8)	0.01	8 (4.7)	8 (88.8%)
PsA n=1		CDAI	32 (0)	3 (0)	NI		NI	1 (100%)
	IgG4_RD	C/F	dyspnea	improved	improved		NI	1 (100%)
Other n=3	GPA	C/F	Subglottic stenosis	stable	stable		inactive	1 (100%)
	AOSD	CDAI	43 (0)	40 (0)	35 (0)		41 (0)	0
	PM n=4	CK U/L	1955 (1365)	2352 (1695)	1520 (1907)	0.72	(1227, 0)	0
IIM n=5	ILD n=1	FVC (L)	2.5 (0)	2.47 (0)	2.8 (0)		2.8 (0)	Mild improvement

	AIHA n=3	Hb g/dl	6.8 (2.9)	11.6 (3)	-	0.2	13.4 (0)	1 (100%)
	Thrombocytopenia n=5	Plt x 10^9/L	38.6 (32.6)	301.8 (75.4)	226.5 (136.8)	0.02	119.5 (115.3)	5 (100%)
SLE								
n=17	Pneumonitis, SLS n=3	FVC% predicted	45.7 (5.6)	50.7 (3.3)	44.7(0)	0.9	47.4 (0)	2/3 (66.7%)
	Pancytopenia n=1	Periph blood count (Hb/WCC/Plt)	7.8/1.2/102	11.3/ 1.53/ 198	NI		NI	I (100%)
	SLE-Arthritis n=1	Active joint count	8 (0)	2 (0)	2 (0)		NI	1 (100%)
	LN n=2	UPCR	0.7 (.4)	0.7 (.5)	0.8 (0)	0.9	NI	0
	NPSLE n=1	C/F	Confusion	improved				1 (100%)
	Pulmonary vasculitis n=1	C/F	Hypoxia	improved				1 (100%)
	M Gravis	MGCS	23 (0)	1 (0)	NI		NI	Improved
Neurol	MS	EDSS	35 (0)	35 (0)	NI		NI	Stable

ogy		Valid						
n=4	NMO	C/F	Weak	Weak	NI		NI	0
	PM	CK U/L	1795 (0)	2812 (0)	962 (0)		NI	100%
Ophth almolo gy n=25	Uveitis n=18	VA	0.3 (.2)	0.5 (.3)	0.7 (.3)	0.001	0.3 (0)	13 (72.2%)
	Scleritis n=5	Pain	Pain +++	Improved in 4/5	No pain in 4		No pain in 4I	4 (80%)
	Ulcerativ e keratitis n=1	C/F	Inflammation	No inflammation	No inflammation		No inflammation	1 (100%)
	Optic neuritis n n=1	VA	1 (0)	1 (0)				1 (100%)
Gastro entero logy n=31	CD n=26	C/F	D=8, PAD(F)=10, CDF=11, BIS=4	D=3, PAD(F)=3, CDF=1, BIS=2,	D=2 PAD=2, CDF=1, BIS=1,	-	D=1, PAD(F)=1 CDF=1 BIS=0	20 (77%)
	UC n=5	C/F	UCF=5	CWC= 4 Active=1	CWC=4 Active=1	-	CWC=4 Active=1	4 (80%)

*p-value comparing baseline and 12-month

Definitions of satisfactory response were disease-specific as follows: Satisfactory response in **SpA: BASDAI score < 4; **Antisynthetase syndrome:** improvement in FVC; **AOSD:** CDAI ≤10; **CD and UC:** improvement in clinical features (diarrhoea, bloody stool, abdominal cramps, arthralgia, nausea and vomiting, fistula, perianal discharge, perianal abcess, wound dehiscence); **GPA:** improvement in subglottic stenosis; **IgG4-RD:** improvement in wheeze and breathing difficulty; **IIM:** decreased CK and clinically improved in CSM; **M Gravis:** improvement in MGCS and C/F; **MS:** improvement in EDSS score and C/F; **NMO:** improved weakness; **PM:** improvement in CK and MMT; **PSO:** BSA%≤10%; **PsA**: CDAI ≤10; **RA:** remission or low disease activity (CDAI ≤10); **SLE arthritis:** active joints count ≤2; **SLE AIHA:** return Hb to normal; **SLE Pancytopenia:** improvement in Hb, Plt and WBCs; **SLE Pulmonary Vasculitis:** improved in cough and air entry; **SLE Pneumonitis, SLS:** improvement in FVC; **SLE thrombocytopenia:** increased platelet > 100 X 109/L; **Uveitis and Optic neuritis:** improvement of VA; **Ulcerative Keratitis:** improvement in vision and inflammation).

Abbreviations: **AOSD**: Adult Onset Still Diseases; **BASDAI**: Bath Ankylosing Spondylitis Disease Activity Index; **BASFAI**: Bath Ankylosing Spondylitis Functional Index**; BIS**: Blood in stool; **BSA%:** Body Surface Area %; **CD:** Crohn`s disease; **CDAI:** Clinical Disease Activity Index; **CDF:** CD flare; **C/F:** clinical features**; CWC:** Clinically well controlled; **D:** Diarrhoea; **Hb:** Haemoglobin; **CK**: Creatine Kinase; **CRMO**: Chronic Recurrent Multifocal Osteomyelitis; **EDSS**: Expanded Disability Status Scale**; FVC:** Forced Vital Capacity: I**gG4-RD:** Immunoglobulin 4 Related Diseases**; IIM**: Idiopathic inflammatory myopathy; **ILD**: Interstitial Lung Disease; **JDM:** Juvenile Dermatomyositis**; JIA:** Juvenile Idiopathic Arthritis; **LN:** Lupus Nephritis; **M Gravis**: Myasthenia Gravis; **MGCS**: Myasthenia Gravis Composite Score**; MMT:** Manual Muscle testing**; MS**: Multiple Sclerosis; **NI:** Non Indicated; **NMO**: Neuromyelitis Optica; **NPSLE:** Neuro-Psychiatric SLE; **PAD(F):** Perianal discharge and fistula: **Plt:** platelet; **PsA**: Psoriatic Arthritis; **PM:** Polymyositis; **PSO:** Psoraisis**; RA:** Rheumatoid Arthritis**; SpA:** Spondylarthroses; **SD:** Standard Deviation; **SLE:** Systemic Lupus Erythematosus; **SLS:** Shrinkage Lung Syndrome; **TCZ:** Tocilizumab; **TNFi:** Tumour Necrosis Factor Inhibitor; **UC:** Ulcerative Colitis; **UCF:** Ulcerative colitis Flare; **VA:** Visual Activity; **WBCs**: White Blood Cells.

Table 3: Outcomes in paediatric patients treated with bDMARDs

Disease		**Outcome tool**	**Baseline (mean, (SD))**	**6 months (mean, (SD))**	**12 months (mean, (SD))**	**p-value****	**24-months (mean, (SD))**	**No (%) with satisfactory response***
JIA n=26	JIA	cJDAS-11	6.1 (2.6)	1.9 (1.8)	1.1 (1.6)	<0.0001	0.9 (1.1)	22 (84.6%)
Vasculitis n=3	MPA-ILD n=1	FVC (L)	2.0	Good response				1 (100%)
	MPA-CN n=1	Creatinine umol/L	117		86			1 (100%)
	PAN n=1	C/F	panniculitis	Good response	Good response		No new lesions With healing nodules	1(100%)
Others n=4	AIIS n=1	C/F	Rash, panniculitis	No new rash	Suppurative otitis media		Improved	1 (100%)
	Sweet	C/F$	Erythematous	No new				1 (100%)

syndrome n=1		rash	active lesions				
CRMO n=1	C/F	Flare > 3 lesions	ongoing active lesions				Slight improvement
JDM n=1	CK U/L	627 (0)	1049 (0)	1149 (0)		169 (0)	0

***Satisfactory response in JIA:** remission or low disease activity (cJADAS-10 less or = 1.5 in Oligo JIA, less or =.2.5 in Poly JIA); **JDM:** decreased CK and clinically improved in CSM: **MPA-ILD:** Improvement in FVC: **MPA-CN:** improvement in Creatinine; **PAN-Panniculitis**: resolve of skin lesions; **AIIS:** resolved of the rash and Otitis media; **Sweet Syndrome:** resolved of skin lesions; **CRMO:** number of infected areas.
**p-value comparing baseline and 12-month

Abbreviations: AIHA: Auto-immune Haemolytic anaemia; **AIIS:** Autoimmune Inflammatory Syndrome; **CDAI:** Clinical Disease Activity Index; **C/F:** Clinical features; **CK:** Creatine Kinase; **cJADAS-10:** clinical JIA Disease Activity Index 10 joints count; **CRMO:** Chronic Recurrent Multifocal Osteomyelitis; **JDM:** Juvenile Dermatomyositis; **JIA:** Juvenile Idiopathic Arthritis; **LN:** Lupus Nephritis; **MPA-CN:** Microscopic Polyangiitis associated Crescentic Nephritis; **MPA-ILD:** Microscopic Polyangiitis associated Interstitial Lung Disease; **NPSLE:** Neuro-Psychiatric Systemic Lupus erythematosus; **PAN:** Polyarteritis Nodosa; **SD:** Standard Deviation.

Table 4: Screening prior to prescribing bDMARDs

	Screening procedure	Positive or abnormal	Negative or normal	Not performed (n, %)
TB	History of TB	12/151 (7.9)	139/151 (92.1%)	0
	CXR	5/151 (3.3%)	140/151 (92.7%)	6 /151(4%)
	TST	10/151 (6.6%)	45/151 (29.8%)	96/151 (63.6%)
	TST (Patients on TNFi)	9/88 (10%)	28/88 (32%)	51/88 (58%)
	INH prophylaxis all bDMARDs	81 (53.6%)		70/151 (46.4%)
	Long term INH prophylaxis (Patients on TNFi)	44/88 (54.3%)		
	6-month INH prophylaxis (Patients on TNFi)	7/88 (8%)		
Hepatitis B	HBsAg	2/151 (1.3%)	91/151(60.3%)	58/151 (38.41 %)
	Patients on RTX	0	33/51 (64.7)	18/51 (35.3%)
	HBcab	2 (1.3%)	40 (26.5%)	109 (72.2%)
	Patients on RTX	1/51 (2%)	14/51 (27.4%)	36 (70.6%)
Hepatitis C		0	81(53.6%)	70 (46.4%)
HIV		3 (2%)	85(56.3%)	63 (41.7%)

Abbreviations: **bDMARD:** biologic disease-modifying anti-rheumatic drugs; **CXR:** Chest X-Ray; HBsAg**:** HBV Surface Antigen; **HBcab:** HBV core antibody; **HIV:** Human Immune Virus; **INH:** Isoniazid; pts: patients; **TB:** TB: **TST:** Tuberculin Skin Test; **TNFi:** Tumour Necrosis Factor-alpha inhibitor.

Table 5: Side effects, discontinuation and adherence to bDMARDs

Problem	Details	Number (%)
Adverse reaction	Mild reaction (rash and itching)	14 (7.7%)
n=30 (16.5%)	Severe allergic reaction	3 (1.6%)
	Infection – all	10 (5.5%)
	- TB	2 (1.1%)
	- PCP	1 (.5%)
	- Septicemia	3 (1.6%)
	- Varicella	2 (1.1%)
	- Mild infection	2 (1.1%)
	Other - ILD, elevated liver enzymes	3 (1.6%)
Temporarily stopped	Infection	2 (1.1%)
n=8 (5.3%)	Other Adverse Events	2 (1.1%)
	Poor adherence	1 (.5%)
	Financial or social	1 (.5%)
	Clinical Trial stopped	2 (1.1%)
bDMARDs discontinued	Poor response	4 (2.2%)
n=18 (11.9%)	Remission	1 (.5%)
	Infection	5 (2.7%)
	HIV positive	1 (.5%)
	Other Adverse Events *	2 (1.1%)
	Lost to follow up or defaulted treatment	4 (2.2%)
	Medical aid stopped	1 (.5%)
Poor adherence	Failed to collect medication or attend the	17 (9.3%)
n=18 (9.9%)	clinic	
	Unable to afford bDMARD	1 (.5%)

* 1 elevated liver enzymes, I worsening ILD. 1 reaction to rituximab

Abbreviations: **bDMARDs:** biologic Disease-Modifying Anti-Rheumatic Drugs, **ILD:** Interstitial Lung Disease, **PCP:** Pneumocystis Carinii Pneumonia.

Table 6 (supplementary): Table 6 Patients using more than 1 bDMARD (total 27 bDMARDs)

Diagnosis	bDMARD 1 n= 27	Reason for change	n (%)	bDMARD 2 n= 27	Respond n (%)
JIA n=1, **PSO** n=1, **AS** n=1, **IIM** n=1, **Uveitis** n=1	TNFi n=10	Poor response	10 (38.5 %)	TNFi n=6 Rituximab n=2 Tocilizumab n=1 Abatacept n=1	7/10 (70%)
JIA n=1	Etanercept n=2 Anakinra n=1	Adverse Event (infection)	3 (11.1%)	Tocilizumab n=2 Rituximab n=1	3/3 (100%)
CD n=1, **JIA n=1, PSO n= 1**, **UC n=1**, **SLE n=1**	TNFi n=3 Tocilizumab n=1	Adverse Event (Infusion reaction)	5 (18.5%)	TNFi n=3 Anakinra n=1 RTX n=1	5/5 (100%)
SLE n=1 **PSO** n=1 **AIIS** n=1	TNFi n=1 Tofacitinib n=1	Not documented	3 (12.5%)	TNFi n=3	3/3 (100%)
PSO n=1	Infliximab	Medical aid stopped	n=1	Etanercept	Partially improved
PSO n=1	Adalimumab	Clinical Trial stopped	n=1	Infliximab	1 (100%)
PSO n=1	Etanercept	Cost	n=1	Etanercept	1 (100%)

CD	n=1	Infliximab	Patient preference	n=1	Adalimumab	1 (100%)
CD	n=1	Infliximab	not approved by pharmacy	n=1	Adalimumab	0

Abbreviations: AIIS: Autoimmune Inflammatory Syndrome; AS: Ankylosing spondylitis; **CD:** Crohn`s disease; **JIA:** Juvenile Idiopathic Arthritis; **IIM:** idiopathic immune-mediated myopathy; **PSO:** Psoriasis; **SLE**: systemic lupus erythematosus; **US**: ulcerative colitis.

Table 7 (supplementary): Patients using more than 2 bDMARD (total 5 bDMARDs)

Diagnosis	bDMARD 1	Reason for change	n (%)	bDMARD 2	Reason for change	n (%)	bDMARD 3	Response n (%)
JIA	Etanercept Golimumab	Poor response	2	Adalimumab Rituximab	Poor response	2	Tocilizumab	2 (100%)

Abbreviations: JIA: Juvenile Idiopathic Arthritis.

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