Multiple Sclerosis and Related Disorders 2021

Can rheumatologists stop causing demyelinating disease?

David Baker[1,] Charalambos Hadjicharalambous[1], Sharmilee Gnanapavan[1,2], Gavin Giovannoni[1,2]

[1]Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, United Kingdom,

[2]Clinical Board:Medicine (Neuroscience), The Royal London Hospital, Barts Health NHS Trust, London, United Kingdom

Correspondence: David Baker, Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, E1 2AT, United Kingdom. Email. david.baker@qmul.ac.uk

Abbreviations CNS: central nervous system (CNS), cerebrospinal fluid (CSF), DMARDS: disease modifying anti-rheumatoid drugs: multiple sclerosis MS, rheumatoid arthritis, TNF:tumour necrosis factor

Summary

Background: Perhaps the most informative experiments in human disease are clinical trials and notably, responses to specific therapies can be highly-informative to help understand disease pathogenesis. There are reagents that inhibit a variety of different autoimmune conditions, such as CD20 memory B cell depleters that are active in both multiple sclerosis (MS), rheumatoid arthritis (RA) and other conditions, suggesting influences on common immune mechanisms in different diseases. However, a notable exception seemed to be the use of tumour necrosis factor (TNF) inhibitors that limits RA, yet seem to, rarely, trigger demyelination and induce MS. This was first seen with TNF-inhibiting monoclonal antibodies and TNF-receptor-immunoglobulin fusion proteins. However, this is also seen with tyrosine and Janus kinase inhibitors that inhibit RA, yet induce demyelinating disease in some individuals

Purpose: To provide an overview, from a B cell centric perspective, that may underpin the biology that links arthritis treatments to the development of demyelinating disease.

Conclusions: It is apparent that the disease modifying anti-rheumatoid drugs that cause demyelination share a number of common features. These agents tend to inhibit TNF-receptor signalling, augment or exhibit limited inhibitor activity on class-switched memory B cells and importantly appear to be relatively excluded from the central nervous system (CNS). They will thus not target ectopic B cell follicles in the CNS, unlike that occurring in peripheral autoimmunity as seen with anti-TNF treatments in RA. Agents such as ibudilast and some Janus kinase inhibitors that inhibit TNF and clearly penetrate the CNS do not appear to induce demyelination and may even be neuroprotective. It remains to be established whether selection or development of CNS penetrant agents may avoid CNS-complications of treatments for RA. Clearly, further studies are warranted

Key words: autoimmunity, demyelination, multiple sclerosis, rheumatoid arthritis, tumour necrosis factor, tyrosine kinase, inhibitor Janus kinase

1. Introduction. Multiple sclerosis (MS) is the major demyelinating disease of the central nervous system (CNS) that affects about 2-3 million people worldwide [1]. This is typically characterised by relapsing neurological attacks associated with peripheral inflammatory, mononuclear cell responses entering the CNS, which lead to lesion formation and nerve damage [1]. The inflammatory response becomes sequestered within the CNS and also appears to drive a slow, glial-associated, neurodegeneration, that becomes clinically apparent as the compensatory mechanisms become exhausted [1]. These processes both occur from disease onset until death, but to date therapy has focused on the inhibition of the peripheral immune response to inhibit relapsing and active or relapsing progressive MS [1,2].

2 Routes to understanding autoimmunity and CNS demyelination. Although, there are many routes to understand MS, ideas based on animal studies have perhaps been the most influential in generating ideas of common treatment modalities in autoimmunity. This has led to a focus on targeting CD4 Th1/Th17 responses [3,4]. However, the most informative experiments that lead to understanding of MS are human clinical trials. Positive and well-constructed and implemented, negative trials are highly informative [5-7]. As such it appears that all agents that inhibit relapsing MS, serve to limit the accumulation of memory B cell subsets into the CNS [8,9]. This is consistent with the aetiology, genetics, pathology of MS and the hierarchy of response to therapy [9] and contrasts with the limited inhibitory effect of CD20-B cell depletion in animal models of MS, which are largely CD4 T cell-mediated [10]. CD20 depleting antibodies are licenced for both rheumatoid arthritis and MS [11,12], supporting the view that there are common pathways in autoimmunity (**Figure 1**).

However, in contrast to the potent inhibitory effect of tumour necrosis factor (TNF) inhibitors in rheumatoid arthritis and promise in animal models of MS [13-15], peripheral TNF inhibition failed to inhibit or exacerbated MS in some people [16-19]. Furthermore, peripheral nerve and CNS demyelination appeared to be a side effect of the use of TNF-specific antibodies and TNF-receptor immunoglobulin fusion proteins [16-19]. In addition, it has been found that MS-associated genetic variants (TNFRSF1A, CD120a), which supports expression of a soluble form of TNF-receptor I to reduce TNF activity, can worsen CNS inflammation and support the observations with TNF-inhibitors [20]. Whilst there are a number of different potential explanations for this activity [17, 18], consistent with the view that disease modifying treatments (DMT) for MS inhibit memory B cells, TNF-specific antibodies failed to inhibit or increase the absolute number of class switched memory B cells in some individuals [21, 22]. However, as arthritis, MS and other autoimmune conditions, respond to CD20-depleting antibodies in a manner that seems to relate to memory B cell depletion [8,9,23,24], suggests that other mechanisms are needed to explain the dichotomy in disease inhibition by TNF blockers in rheumatoid arthritis compared with MS.

Interestingly, demyelination is seen as a rare side-effect by an increasing number of other disease modifying anti-rheumatoid drugs (DMARDS) used in arthritic diseases [25] and

therefore interrogation of the properties of these agents may identify common mechanisms that explain the response to therapy of DMARDS and their capacity to induce MS. It was hypothesised that CNS-penetration and lack of effective central TNF inhibition may be associated with failure to control CNS demyelinating disease [15]. Although alternative explanations have been made [17, 18], a B cell centric mechanism is explored that can accommodate the clinical observations

3.1 Tumour necrosis factor inhibitors. Although TNF blockers, such as infliximab, adalimumab and etanercept are potent inhibitors of rheumatoid arthritis, their use has increasingly been associated with the development of demyelinating disease [17-19]. These include: MS, optic neuritis, acute transverse myelitis, as well as peripheral nervous system disorders such as Guillain-Barré syndrome, Miller Fisher syndrome, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy with conduction block, mononeuropathy multiplex, and axonal sensorimotor polyneuropathy, although whether these are coincidental or side-effects is unclear [17-19]. Antibodies and immunoglobulin fusion proteins have a low capacity to cross the blood brain barrier and therefore are unlikely to have significant on-target effects in the CNS compared to peripheral issues [26]. Indeed, it has been reported that TNF-inhibiting monoclonal antibodies do not appear to inhibit central TNF levels [27, 28], in contrast to TNF inhibition in arthritic joints [29] There are a number of possible explanations that account for TNF-induced demyelination [17,30]. Examination of the impact of other DMARDS may provide insight into possible effects of anti-TNF reagents.

3.2 Tyrosine kinase inhibitors. Imatinib mesylate is a first generation tyrosine kinase inhibitor that acts on the breakpoint cluster region-Abelson tyrosine kinase and other kinases involved in signal transduction that can slow cell growth or result in programmed cell death of certain types of cancer cells and has been used as a DMARD [31-33]. This agent can inhibit TNF production [34, 35] and has been associated with the development of CNS demyelination [36,37]. This potential problem is also seen with a number of second generation tyrosine kinase inhibitors where peripheral and central demyelinating disease is evident in some people treated with nilotinib [38,39] and peripheral demyelination has been associated with use of dasatinib [40,41].

Tyrosine kinase inhibition can be associated with lower immunoglobulin level and there was a modest reduction of class-switched IgG memory B cells with imatinib, nilotinib and dasatinib treatment [42]. However, they also inhibit Bruton's tyrosine kinase, which can block B cell function [42]. It is evident that imatinib is a p-glycoprotein (ABCB1) substrate and is largely excluded from the CNS [43, 44]. Likewise, nilotinib is largely excluded from the cerebrospinal fluid (CSF) with a CSF/plasma ratio of about 0.19%-0.53% [45,46]. Although it has been reported that dasatinib crosses the blood-brain barrier [47], like imatinib, it is an ABCB1 and ABCG2 substrate that limits penetration and the drug exhibits relatively low permeability with a CSF/plasma ratio of about 3.9% [48,49]. As such the CNS potency [47] over that reported

for imatinib may relate to the higher potency at the target rather than enhanced CNS penetration [49]. Therefore, there appears to be mechanistic similarities with TNF-specific neutralizing antibodies.

3.3 Janus kinase inhibitors. JAK kinases (JAK1, JAK2, JAK3 and TYK2 tyrosine kinase two) are a group of tyrosine kinases that transduce cytokine-mediated signals notably IL-4, IL-6, IL-7, IL-9, IL-15, IL-21, and interferon gamma [50] and a number have been used in rheumatoid arthritis [50,51]. Tofacitinib citrate which inhibits JAK1/JAK3 is approved for treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response to, or who are intolerant of, methotrexate [50]. Tofacitinib has recently been reported to induce CNS demyelination [52], again treatment can lead to a reduction in TNF production, although this effect is not probably direct [50,53]. Ruxolitinib, a JAK1/JAK2 inhibitor has been associated with a few case reports of peripheral neuropathy [54, 55]. Baricitinib is an JAK1/JAK2 inhibitor is another DMARD that likewise can inhibit TNF but this does not seem to induce CNS demyelination [50,56]. Both tofacitinib and baricitinib are associated with increases in class switched memory B cells in some individuals [57,58]. However the notable difference between these agents are that there is CNS penetration of baricitinib, with a cerebrospinal fluid:plasma ratio of about 20%, compared with about 0.1% for tofacitinib and 3.5% for ruxolitinib [59].

3.4 Interleukin-six receptor inhibitors. Tocilizumab is a humanized monoclonal antibody against soluble and membrane-bound human interleukin-6 receptors that is used in moderate to severe rheumatoid arthritis [60]. Whilst use of this DMARD has also been associated with the development of MS [61], this is a rare event and may not be causally related [62]. Although the mechanistic action is distinct from TNF-inhibitors there are some functional similarities. This antibody can inhibit the production of pro-inflammatory cytokines, including interleukin 6 and indirectly TNF [63]. Furthermore, it either fails to inhibit or enhances the absolute number of class-switched memory B cells and plasmablasts [61,64], but could reduce peripheral plasma cell activity [65]. Indeed, this may offer benefit in neuromyelitis optica spectrum disorders and myelin oligodendrocyte glycoprotein IgG associated disorder associated with peripheral and central neuro-antigen specific IgG that can induce demyelinating diseases [66-68]. This is supported by the findings with satralizumab that also targets the interleukin-6 receptor and multiple sclerosis was not a noted side-effect [69,70]. However, in the case report where MS developed, it occurred many years after initiation of tocilizumab [61] suggesting this is unlikely to be a major problem [62]. Indeed, it has been suggested it could be beneficial [71].

3.5 TNF-inhibiting phosphodiesterase four inhibitors. As soon as TNF-inhibitors were suggested to be important in the control of experimental neuroimmunological disease, it was reported that phosphodiesterase inhibitors were potent TNF/Lymphotoxin inhibitors that could have value in controlling MS [72-74]. Rolipram, pentoxifylline and ibudilast, which are not approved for use in arthritis, have all been reported to penetrate the central nervous system

[75, 76]. Whilst a clinical trial in MS with rolipram was terminated due to apparent lesional enhancement and augmentation of CD86+ (memory) B cell activity [77], significant lesion enhancement was not evident in studies with ibudilast [78, 79] and pentoxifylline does not also appear to worsen demyelinating disease [80,81]. Although CNS penetration of rolipram in rodents occurs, this is less evident at human relevant doses [76], which are restricted by dose-related gastrointestinal and emetic side-effects that do not affect rodents as they cannot vomit. Therefore, the degree of central TNF inhibition by rolipram is unknown. Ibudilast has been used at much higher doses than rolipram in multiple sclerosis [77-79,82, 83]. Ibudilast may induce neuroprotective effects in MS [79,83] and has been reported to inhibit neuropathic pain in rodents [75]. However, not all clinical results are consistent with the views presented here and apremilast is a DMARD that can be used in psoriatic arthritis that inhibits TNF activity [84, 85]. However, this is reported to have a brain/plasma concentration ratio of ≤0.1 and is unlikely to enter the brain [85] and in contrast to other peripherally active TNF inhibitors, it has not yet been associated with development of demyelinating disease.

3.6 Immune checkpoint inhibitors same result, different mechanism? There are other classes of agents that may cause the development of demyelinating diseases and this includes a variety of immune-checkpoint inhibitors, developed for the treatment of cancers [86]. These include nivolumab and pembrolizumab that block the programmed cell death-1 (PD-1/CD279) receptor, atezolizumab that blocks the programmed cell death ligand one (PD-L1/CD274) and ipilimumab that blocks cytotoxic T lymphocyte antigen four (CTLA4/CD152), notably on T and B cells [86]. Immune checkpoint inhibitors are thought to act by releasing T cells from inhibitory regulation and apoptotic pathways [87]. Blockade of PD-1 or CTLA4 with antibodies has generally had minimal impact on memory B cells [88]. However, adverse immune reactions have been associated with enhanced memory B cell ($CD21^{low}$) subset/plasmablast responses [88]. Again being antibodies, they will have limited penetration into the central nervous system and thus have some similarities with the tyrosine kinase inhibitors. However, such immune-checkpoint inhibitors may augment TNF responses and induce arthritis generally lacking rheumatoid factor [89,90]. Importantly, both checkpoint inhibitor-induced arthritis and demyelinating conditions may respond to TNF-blocking therapy [91, 92]. This suggests that the aetiological demyelinating mechanisms of immune checkpoint inhibitors, such as through influences on immune regulation are distinct from the demyelinating DMARDS, associated with the use of TNF-inhibitors.

4. Inhibition of central nervous system TNF as a means to halt demyelinating disease. Whilst targeting peripheral B cells in arthritis, MS and other diseases, notably cells within the memory B cell population, inhibits disease activity in established autoimmunity [23, 24]. Synovial B cells serve to activate autoreactive T cells [93] and therefore events within the CNS are likely to be key to the treatment of MS. Tumour necrosis factor alpha and particularly TNF beta (lymphotoxin) are important in the formation and maintenance of lymphoid architecture and B cell follicles [94]. Ectopic lymphoid structures develop in arthritic joints, but are present

in sites of inflammation in target tissues in a number of autoimmune diseases including Sjögren's syndrome, myasthenia gravis, and systemic lupus erythematosus [94]. Importantly, they occur in MS where they may play a role in chronic neurodegeneration [94-96]. Production of oligoclonal antibody is a characteristic, early feature of B cells sequestered with the CNS that may produce cytokines and antibodies that contribute to cortical and white matter lesions and glia activity possibly via Fc receptor activation [95,96]. Therefore, it may be of relevance that TNF-blockade can reverse formation of follicles in the joints in arthritis, at least in a subset of patients, would suggest that TNF-α can play a non-redundant role in ectopic follicle maintenance over and above lymphotoxin [97]. It seems that TNF inhibition blocks the induction of T cell-dependent humoral responses [98]. Importantly, successful anti-TNF immunotherapy is associated with reductions in synovial plasma cell numbers and ectopic follicles [99]. Therefore, lack of sufficient TNF-inhibition within the CNS to block local B cell function may be key feature for augmentation of demyelinating disease (**Figure 1**).

5. Future Perspectives. Whilst there are other explanations in addition to activities on B cells, such as the inability to block T cells or to control latent infections that may account for activity [17, 100], it remains to be established if TNF can be specifically-targeted within the CNS to provide benefit in MS. Perhaps there could be selective targeting of specific TNF alpha ligands and/or TNF receptor isoforms within the CNS, in particular soluble TNFa and TNFR1, while sparing transmembrane TNFa-TNFR2/CD120b signalling pathways that may promote remyelination, repair and neuroprotection [101,102]. This may be less likely to result in new onset or worsening demyelination compared to non-selective inhibition. Whilst it is likely that agents targeting TNF pathways will be generated for use in RA [101], it remains to be seen whether fear of targeting TNF-pathways in MS, created by the use of non-selective TNF inhibitors, can be overcome by a better understanding of the beneficial and deleterious effects of selective inhibition of the various TNF-related biological pathways [102]. Likewise, it remains to be established whether selection or development of CNS-penetrant agents, such as small molecules [101], may avoid the rare CNS-complications of treatments for RA. Clearly, further studies are warranted

Funding. The study received no funding.

Declaration of Interests. The research was conducted in the absence of any commercial or financial relationships. However, DB has received consultancy and presentation fees from Canbex Therapeutics, InMune Bio, Lundbeck, Novartis, Merck, Roche and Teva. CH has nothing to declare. SG has received travel support, consultancy fees or grant support from Biogen, Novartis, Teva, Pfizer, and Takeda. GG has received consultancy, presentation fees or grants from Abbvie Biotherapeutics, Actelion, Atara Bio, Biogen, Canbex, Celgene, Genentech, Japan Tobacco, Merck, Novartis, Roche, Sanofi-Genzyme, Synthon, Takeda, and Teva.

References

1. Dobson R, Giovannoni G. Multiple sclerosis - a review. Eur J Neurol. 2019; 26:27-40.

2. Giovannoni G, Butzkueven H, Dhib-Jalbut S, Hobart J, Kobelt G, Pepper G, Sormani MP, Thalheim C, Traboulsee A, Vollmer T Brain health: time matters in multiple sclerosis. Mult Scler Relat Disord. 2016; 9 Suppl 1:S5-S48.

3. Moser T, Akgün K, Proschmann U, Sellner J, Ziemssen T. The role of TH17 cells in multiple sclerosis: Therapeutic implications. Autoimmun Rev. 2020; 19:102647.

4.Kunkl M, Frascolla S, Amormino C, Volpe E, Tuosto L.T Helper Cells: The Modulators of inflammation in multiple sclerosis.Cells. 2020;9(2):482.

5. Kleinschnitz C, Meuth SG, Wiendl H The trials and errors in MS therapy. Int MS J. 2008;15:79-90.

6. Pfeuffer S, Ruck T, Kleinschnitz C, Wiendl H, Meuth SG. Failed, interrupted and inconclusive trials on relapsing multiple sclerosis treatment: update 2010-2015.Expert Rev Neurother. 2016; 16:689-700.

7.Rolfes L, Pawlitzki M, Pfeuffer S, Huntemann N, Wiendl H, Ruck T, Meuth SG Failed, Interrupted, or Inconclusive Trials on Immunomodulatory Treatment Strategies in Multiple Sclerosis: Update 2015-2020. BioDrugs. 2020;34:587-610

8. Baker D, Marta M, Pryce G, Giovannoni G, Schmierer K Memory B cells are major targets for effective immunotherapy in relapsing multiple sclerosis. EBioMedicine. 2017; 16:41-50.

9. Baker D, Pryce G, Amor S, Giovannoni G, Schmierer K. Learning from other autoimmunities to understand targeting of B cells to control multiple sclerosis. Brain. 2018; 141:2834-2847.

10. Sefia E, Pryce G, Meier UC, Giovannoni G, Baker D. Depletion of CD20 B cells fails to inhibit relapsing mouse experimental autoimmune encephalomyelitis. Mult Scler Relat Disord. 2017;14:46-50

11.Cohen SB, Emery P, Greenwald MW, Dougados M, Furie RA, Genovese MC, Keystone EC, Loveless JE, Burmester GR, Cravets MW, Hessey EW, Shaw T, Totoritis MC; REFLEX Trial Group. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum. 2006; 54:2793-806

12. Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung HP, Hemmer B, Lublin F, Montalban X, Rammohan KW, Selmaj K, Traboulsee A, Wolinsky JS, Arnold DL, Klingelschmitt G, Masterman D, Fontoura P, Belachew S, Chin P, Mairon N, Garren H, Kappos L; OPERA I and OPERA II Clinical Investigators. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. N Engl J Med. 2017; 376:221-234.

13. Elliott MJ, Maini RN, Feldmann M, Kalden JR, Antoni C, Smolen JS, Leeb B, Breedveld FC, Macfarlane JD, Bijl H, et al. Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis. Lancet. 1994;344:1105-10.

14. Ruddle NH, Bergman CM, McGrath KM, Lingenheld EG, Grunnet ML, Padula SJ, Clark RB. An antibody to lymphotoxin and tumor necrosis factor prevents transfer of experimental allergic encephalomyelitis. J Exp Med. 1990;172:1193-200

15. Baker D, Butler D, Scallon BJ, O'Neill JK, Turk JL, Feldmann M. Control of established experimental allergic encephalomyelitis by inhibition of tumor necrosis factor (TNF) activity within the central nervous system using monoclonal antibodies and TNF receptor-immunoglobulin fusion proteins. Eur J Immunol. 1994;24:2040-2048

16. van Oosten BW, Barkhof F, Truyen L, Boringa JB, Bertelsmann FW, von Blomberg BM, Woody JN, Hartung HP, Polman CH. Increased MRI activity and immune activation in two multiple sclerosis patients treated with the monoclonal anti-tumor necrosis factor antibody cA2. Neurology. 1996; 47:1531-4.

17. Kemanetzoglou E, Andreadou E. CNS Demyelination with TNF-alpha Blockers. Curr Neurol Neurosci Rep. 2017; 17:36.

18. Kumar N, Abboud H. Iatrogenic CNS demyelination in the era of modern biologics. Mult Scler. 2019; 25:1079-1085

19. Taylor TRP, Galloway J, Davies R, Hyrich K, Dobson R. Demyelinating events following initiation of anti-TNFα therapy in the British Society for Rheumatology biologics registry in rheumatoid arthritis. Neurol Neuroimmunol Neuroinflamm. 2021;8:e992.

20. Gregory AP, Dendrou CA, Attfield KE, Haghikia A, Xifara DK, Butter F, Poschmann G, Kaur G, Lambert L, Leach OA, Prömel S, Punwani D, Felce JH, Davis SJ, Gold R, Nielsen FC, Siegel RM, Mann M, Bell JI, McVean G, Fugger L. TNF receptor 1 genetic risk mirrors outcome of anti-TNF therapy in multiple sclerosis. Nature. 2012;488:508-511.

21.Leandro MJ. Anti-tumour necrosis factor therapy and B cells in rheumatoid arthritis. Arthritis Res Ther. 2009;11(5):128.

22. Adlowitz DG, Barnard J, Biear JN, Cistrone C, Owen T, Wang W, Palanichamy A, Ezealah E, Campbell D, Wei C, Looney RJ, Sanz I, Anolik JH. Expansion of Activated Peripheral Blood Memory B Cells in Rheumatoid Arthritis, Impact of B Cell Depletion Therapy, and Biomarkers of Response. PLoS One. 2015 Jun 5;10(6):e0128269.

23. Leandro MJ, Cambridge G, Ehrenstein MR, Edwards JC. Reconstitution of peripheral blood B cells after depletion with rituximab in patients with rheumatoid arthritis. Arthritis Rheum. 2006; 54:613-620

24. Novi G, Bovis F, Fabbri S, Tazza F, Gazzola P, Maietta I, Currò D, Bruschi N, Roccatagliata L, Boffa G, Lapucci C, Pesce G, Cellerino M, Solaro C, Laroni A, Capello E, Mancardi G, Sormani M, Inglese M, Uccelli A. Tailoring B cell depletion therapy in MS according to memory B cell monitoring. Neurol Neuroimmunol Neuroinflamm. 2020; 7:e845.

25. Atzeni F, Nucera V, Gerratana E, Cirillo M, Marino F, Miceli G, Sangari D, Boccassini L, Masala IF. Concerns about the safety of anti-TNF agents when treating rheumatic diseases. Expert Opin Drug Saf. 2020 Jun;19(6):695-705

26. Pardridge WM. Blood-Brain Barrier and Delivery of Protein and Gene Therapeutics to Brain. Front Aging Neurosci. 2020;11:373.

27. Andersson M, Svenungsson E, Khademi M, Lampa J, Brundin L, Wallström E. No signs of immunoactivation in the cerebrospinal fluid during treatment with infliximab. Ann Rheum Dis. 2006; 65: 1237–1240.

28. Kikuchi H, Aramaki K, Hirohata S. Effect of infliximab in progressive neuro-Behçet's syndrome. J Neurol Sci. 2008; 272:99-105.

29. Koo BS, Jo S, Kwon E, Shin JH, Hur JW, Kim TH. Effect of biologics in the level of cytokines in the synovial fluid of patients with ankylosing spondylitis. Korean J Intern Med. 2020 ;35: 465-473.

30. Probert L, Eugster HP, Akassoglou K, Bauer J, Frei K, Lassmann H, Fontana A TNFR1 signalling is critical for the development of demyelination and the limitation of T-cell responses during immune-mediated CNS disease. Brain. 2000; 123:2005-19.

31. Vernon MR, Pearson L, Atallah EJ. Resolution of rheumatoid arthritis symptoms with imatinib mesylate. Clin Rheumatol. 2009; 15:26

32. Pereira I, Fialho S, Castro G, Zimmermann A. Imatinib mesylate induces clinical remission in rheumatoid arthritis. Joint Bone Spine. 2010;77:372-373

33. Anagnostou T, Litzow MR. Spotlight on ponatinib in the treatment of chronic myeloid leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia: patient selection and perspectives. Blood Lymphat Cancer. 2017;8:1-9.

34. Wolf AM, Wolf D, Rumpold H, Ludwiczek S, Enrich B, Gastl G, Weiss G, Tilg H. The kinase inhibitor imatinib mesylate inhibits TNF alpha production in vitro and prevents TNF-dependent acute hepatic inflammation. Proc Natl Acad Sci U S A. 2005; 102:13622-13627.

35. Zbaar SA. Serum level of TNF-alpha in patients with chronic myeloid leukemia on Imatinib therapy Tikrit Medical Journal 2017;22:54-60.

36. Rafei H, Jabbour EJ, Kantarjian H, Sinicrope KD, Kamiya-Matsuoka C, Mehta RS, Daver NG, Kadia TM, Naqvi K, Cortes J, Konopleva M. Neurotoxic events associated with BCR-ABL1 tyrosine kinase inhibitors: a case series. Leuk Lymphoma. 2019;60:3292-3295

37. Rotstein DL, Sawicka K, Bharatha A, Montalban X, Lipton JH. CNS demyelination after initiating the tyrosine kinase inhibitor imatinib: A report of two cases. Mult Scler. 2020; 26:1121-1124.

38. Rekhi E, pryce A, Sohal M, Dassan P. CNS demyelination in patients on nilotinib treatment for CML. J Neurol Neurosurg, Psychiat 2016; 87:e1.62-e1.

39. Judge C, Moheb N, Melinosky C. Nilotinib-associated demyelinating disease (p2.2-093). Neurology 2019; 92 (15 Suppl): P2.2-093.

40. Ishida T, Akagawa N, Miyata T, Tominaga N, Iizuka T, Higashihara M, Suzuki T, Miyazaki K. Dasatinib-associated reversible demyelinating peripheral polyneuropathy in a case of chronic myeloid leukemia. Int J Hematol. 2018; 107:373-377

41. Inoue H, Taji H, Yamada K, Iriyama C, Saito T, Kato H, Yanada M, Yamamoto K, Matsukawa N. Dasatinib-induced reversible demyelinating peripheral neuropathy and successful conversion to nilotinib in chronic myelogenous leukemia. Intern Med. 2020; 59(19):2419-2421

42. de Lavallade H, Khoder A, Hart M, Sarvaria A, Sekine T, Alsuliman A, Mielke S, Bazeos A, Stringaris K, Ali S, Milojkovic D, Foroni L, Chaidos A, Cooper N, Gabriel I, Apperley J, Belsey S, Flanagan RJ, Goldman J, Shpall EJ, Kelleher P, Marin D, Rezvani K. Tyrosine kinase inhibitors impair B-cell immune responses in CML through off-target inhibition of kinases important for cell signaling. Blood. 2013;122:227-238.

43. Wolff, NC, Richardson JA, Egorin M, Ilaria RL. The CNS is a sanctuary for leukemic cells in mice receiving imatinib mesylate for Bcr/Abl-induced leukemia. Blood 2003, 101, 5010– 5013.

44. Ammar M, Louati N, Frikha I, Medhaffar M, Ghozzi H, Elloumi M, Menif H, Zeghal K, Ben Mahmoud L. Overexpression of P-glycoprotein and resistance to Imatinib in chronic myeloid leukemia patients. J Clin Lab Anal. 2020; 34:e23374.

45. Reinwald M, Schleyer E, Kiewe P, Blau IW, Burmeister T, Pursche S, Neumann M, Notter M, Thiel E, Hofmann WK, Kolb HJ, Burdach S, Bender HU. Efficacy and pharmacologic data of second-generation tyrosine kinase inhibitor nilotinib in BCR-ABL-positive leukemia patients with central nervous system relapse after allogeneic stem cell transplantation. Biomed Res Int. 2014;2014:637059.

46. The Parkinson Study Group NILO-PD investigators Nilotinib in patients with advanced parkinson's disease: a randomized phase 2a study (nilo-pd). MedRχiv 2020. https://www.medrxiv.org/content/10.1101/2020.05.11.20093146v1.full.pdf

47. Porkka K, Koskenvesa P, Lundan T, Rimpilainen J, Mustjoki S, Smykla R, Wild R, Luo R, Arnan M, Brethon B, Eccersley L, Hjorth-Hansen H, Hoglund M, Klamova H, Knutsen H, Parikh S, Raffoux E, Gruber F, Brito-Babapulle F, Dombret H, Duarte RF, Elonen E, Paquette R, Zwaan, CM, Lee FY. Dasatinib crosses the blood–brain barrier and is an efficient therapy for central nervous system Philadelphia chromosome-positive leukemia. Blood, 2008; 112, 1005–1112.

48. Chen Y, Agarwal S, Shaik NM, Chen C, Yang Z, Elmquist WF. P-glycoprotein and breast cancer resistance protein influence brain distribution of dasatinib. J Pharmacol Exp Ther. 2009;330:956-63.

49. Takahashi N, Miura M, Scott S, Saitoh H, Motegi M, Fujishima N, kameoka Y, Tagawa H, Hirokawa M, Sawada K. Dasatinib cerebrospinal fluid concentration and plasma pharmacokinetics: potential for central nervous system prophylaxis in philadelphia chromosome-positive leukemia. *Blood* 2010:116:1807.

50.Harrington R, Al Nokhatha SA, Conway R. JAK Inhibitors in Rheumatoid Arthritis: An Evidence-Based Review on the Emerging Clinical Data. J Inflamm Res. 2020 Sep 14;13:519-531.

51. Smolen JS, Genovese MC, Takeuchi T, Hyslop DL, Macias WL, Rooney T, Chen L, Dickson CL, Riddle Camp J, Cardillo TE, Ishii T, Winthrop KL. Safety profile of baricitinib in patients with active rheumatoid arthritis with over 2 years median time in treatment. J Rheumatol. 2019; 46:7-18

52. Massoud F, Ismail II, Al-Hashel JY, Abboud H. CNS demyelination during tofacitinib therapy: First report. Mult Scler Relat Disord. 2020;46:102568. doi: 10.1016/j.msard.2020.102568

53. Krueger J, Clark JD, Suárez-Fariñas M, Fuentes-Duculan J, Cueto I, Wang CQ, Tan H, Wolk R, Rottinghaus ST, Whitley MZ, Valdez H, von Schack D, O'Neil SP, Reddy PS, Tatulych S; A3921147 Study Investigators. Tofacitinib attenuates pathologic immune pathways in patients with psoriasis: A randomized phase 2 study. J Allergy Clin Immunol. 2016;137(4):1079-1090.

54. Gonzalez Vicent M, Molina B, Fabregat M, Segura M, Diaz MA. Toxoplasmosis and secondary Guillain-Barré associated with ruxolitinib as graft-versus-host disease treatment. Pediatr Blood Cancer. 2019 Jan;66(1):e27446.

55. Trantham T, Auten J, Muluneh B, Van Deventer HJ. Ruxolitinib for the treatment of lymphoma-associated hemophagocytic lymphohistiocytosis: A cautionary tale. Oncol Pharm Pract. 2020; 26:1005-1008

56. Bronte V, Ugel S, Tinazzi E, Vella A, De Sanctis F, Canè S, Batani V, Trovato R, Fiore A, Petrova V, Hofer F, Barouni RM, Musiu C, Caligola S, Pinton L, Torroni L, Polati E, Donadello K, Friso S, Pizzolo F, Iezzi M, Facciotti F, Pelicci PG, Righetti D, Bazzoni P, Rampudda M, Comel A, Mosaner W, Lunardi C, Olivieri O. Baricitinib restrains the immune dysregulation in patients with severe COVID-19. J Clin Invest. 2020;130:6409-6416.

57. Rizzi M, Lorenzetti R, Fischer K, Staniek J, Janowska I, Troilo A, Strohmeier V, Erlacher M, Kunze M, Bannert B, Kyburz D, Voll RE, Venhoff N, Thiel J. Impact of tofacitinib treatment on human B-cells in vitro and in vivo. J Autoimmun. 2017 Feb;77:55-66

58. Tanaka Y, McInnes IB, Taylor PC, Byers NL, Chen L, de Bono S, Issa M, Macias WL, Rogai V, Rooney TP, Schlichting DE, Zuckerman SH, Emery P. Characterization and changes of lymphocyte subsets in baricitinib-treated patients with rheumatoid arthritis: an integrated analysis. Arthritis Rheumatol. 2018; 70:1923-1932

59. Richardson PJ, Ottaviani S, Prelle A, Stebbing J, Casalini G, Corbellino M. CNS penetration of potential anti-COVID-19 drugs. J Neurol. 2020 Jul;267(7):1880-1882

60. Scott LJ. Tocilizumab: A Review in Rheumatoid Arthritis. Drugs. 2017; 77:1865-1879.

61. Beauchemin P, Carruthers R. MS arising during Tocilizumab therapy for rheumatoid arthritis. Mult Scler. 2016;22(2):254-6

62. Kleiter I, Ayzenberg I, Araki M, Yamamura T, Gold R Tocilizumab, MS, and NMOSD. Mult Scler. 2016; 22:1891-1892.

63. Mizwicki, MT, Fiala, M, Magpantay, L. Tocilizumab attenuates inflammation in ALS patients through inhibition of IL6 receptor signaling. Am J Neurodegener Dis 2012; 1: 305–315.

64. Roll P, Muhammad K, Schumann M, Kleinart S, Einsele H, Dörner T, Tony HP. In vivo effects of the anti-interleukin-6 receptor inhibitor tocilizumab on the B cell compartment. Arth Rheumat 2011; 63:1255.

65. Illei GG, Shirota Y, Yarboro CH, Daruwalla J, Tackey E, Takada K, Fleisher T, Balow JE, Lipsky PE. Tocilizumab in systemic lupus erythematosus: data on safety, preliminary efficacy,

and impact on circulating plasma cells from an open-label phase I dosage-escalation study. Arthritis Rheum. 2010; 62:542-52.

66. Araki M, Matsuoka T, Miyamoto K, Kusunoki S, Okamoto T, Murata M, Miyake S, Aranami T, Yamamura T. Efficacy of the anti-IL-6 receptor antibody tocilizumab in neuromyelitis optica: a pilot study. Neurology. 2014; 82:1302-1306.

67. Zhang C, Zhang M, Qiu W, Ma H, Zhang X, Zhu Z, Yang CS, Jia D, Zhang TX, Yuan M, Feng Y, Yang L, Lu W, Yu C, Bennett JL, Shi FD; TANGO Study Investigators. Safety and efficacy of tocilizumab versus azathioprine in highly relapsing neuromyelitis optica spectrum disorder (TANGO): an open-label, multicentre, randomised, phase 2 trial. Lancet Neurol. 2020;19:391-401

68. Elsbernd PM, Hoffman WR, Carter JL, Wingerchuk DM. Interleukin-6 inhibition with tocilizumab for relapsing MOG-IgG associated disorder (MOGAD): A case-series and review. Mult Scler Relat Disord. 2020 16;48:102696. doi: 10.1016/j.msard.2020.102696.

69. Yamamura T, Kleiter I, Fujihara K, Palace J, Greenberg B, Zakrzewska-Pniewska B, Patti F, Tsai CP, Saiz A, Yamazaki H, Kawata Y, Wright P, De Seze J. Trial of Satralizumab in Neuromyelitis Optica Spectrum Disorder. N Engl J Med. 2019;381:2114-2124.

70. Duchow A, Bellmann-Strobl J. Satralizumab in the treatment of neuromyelitis optica spectrum disorder. Neurodegener Dis Manag. 2021;11:49-59.

71. Hoshino H, Shirai Y, Konishi H, Yamamura T, Shimizu N. Efficacy of tocilizumab for fulminant multiple sclerosis with a tumefactive cervical lesion: A 12-year-old boy. Mult Scler Relat Disord. 2020 Jan;37:101460. doi: 10.1016/j.msard.2019.101460.

72.Sommer N, Löschmann PA, Northoff GH, Weller M, Steinbrecher A, Steinbach JP, Lichtenfels R, Meyermann R, Riethmüller A, Fontana A, et al. The antidepressant rolipram suppresses cytokine production and prevents autoimmune encephalomyelitis. Nat Med. 1995;1(3):244-8.

73. Genain CP, Roberts T, Davis RL, Nguyen MH, Uccelli A, Faulds D, Li Y, Hedgpeth J, Hauser SL. Prevention of autoimmune demyelination in non-human primates by a cAMP-specific phosphodiesterase inhibitor. Proc Natl Acad Sci U S A. 1995;92:3601-5.

74.Fujimoto T, Sakoda S, Fujimura H, Yanagihara T. Ibudilast, a phosphodiesterase inhibitor, ameliorates experimental autoimmune encephalomyelitis in Dark August rats. J Neuroimmunol. 1999 Mar 1;95(1-2):35-42.

75. Ledeboer A, Hutchinson MR, Watkins LR, Johnson KW. Ibudilast (AV-411). A new class therapeutic candidate for neuropathic pain and opioid withdrawal syndromes. Expert Opin Investig Drugs. 2007; 16:935-50.

76. Kraft P, Schwarz T, Göb E, Heydenreich N, Brede M, Meuth SG, Kleinschnitz C. The phosphodiesterase-4 inhibitor rolipram protects from ischemic stroke in mice by reducing blood-brain-barrier damage, inflammation and thrombosis. Exp Neurol. 2013;247:80-90.

77. Bielekova B, Richert N, Howard T, Packer AN, Blevins G, Ohayon J, McFarland HF, Stürzebecher CS, Martin R. Treatment with the phosphodiesterase type-4 inhibitor rolipram fails to inhibit blood--brain barrier disruption in multiple sclerosis Mult Scler. 2009;15:1206-14.

78. Barkhof F, Hulst HE, Drulovic J, Uitdehaag BM, Matsuda K, Landin R; MN166-001 Investigators. Ibudilast in relapsing-remitting multiple sclerosis: a neuroprotectant? Neurology. 2010;74:1033-40

79. Fox RJ, Coffey CS, Conwit R, Cudkowicz ME, Gleason T, Goodman A, Klawiter EC, Matsuda K, McGovern M, Naismith RT, Ashokkumar A, Barnes J, Ecklund D, Klingner E, Koepp M, Long JD, Natarajan S, Thornell B, Yankey J, Bermel RA, Debbins JP, Huang X, Jagodnik P, Lowe MJ, Nakamura K, Narayanan S, Sakaie KE, Thoomukuntla B, Zhou X, Krieger S, Alvarez E, Apperson M, Bashir K, Cohen BA, Coyle PK, Delgado S, Dewitt LD, Flores A, Giesser BS, Goldman MD, Jubelt B, Lava N, Lynch SG, Moses H, Ontaneda D, Perumal JS, Racke M, Repovic P, Riley CS, Severson C, Shinnar S, Suski V, Weinstock-Guttman B, Yadav V, Zabeti A; NN102/SPRINT-MS Trial Investigators. Phase 2 Trial of Ibudilast in Progressive Multiple Sclerosis. N Engl J Med. 2018;379:846-855

80. Friedman JE, Zabriskie J, Bourganskaia E. A pilot study of pentoxifylline in multiple sclerosis. Arch Neurol. 1996;53:956-7.

81. Rieckmann P, Weber F, Günther A, Martin S, Bitsch A, Broocks A, Kitze B, Weber T, Börner T, Poser S Pentoxifylline, a phosphodiesterase inhibitor, induces immune deviation in patients with multiple sclerosis. J Neuroimmunol. 1996; 64:193-200

82. Rolan P, Gibbons JA, He L, Chang E, Jones D, Gross MI, Davidson JB, Sanftner LM, Johnson KW. Ibudilast in healthy volunteers: safety, tolerability and pharmacokinetics with single and multiple doses. Br J Clin Pharmacol. 2008;66:792-801

83. Naismith RT, Bermel RA, Coffey CS, Goodman AD, Fedler J, Kearney M, Klawiter EC, Nakamura K, Narayanan S, Goebel C, Yankey J, Klingner E, Fox RJ; SPRINT-MS investigators. Effects of ibudilast on MRI measures in the phase 2 SPRINT-MS study. Neurology. 2020:10.1212/WNL.0000000000011314.

84. Mavropoulos A, Zafiriou E, Simopoulou T, Brotis AG, Liaskos C, Roussaki-Schulze A, Katsiari CG, Bogdanos DP, Sakkas LI. Apremilast increases IL-10-producing regulatory B cells and decreases proinflammatory T cells and innate cells in psoriatic arthritis and psoriasis. Rheumatology. 2019; 58:2240

85. Jung YJ, Tweedie D, Scerba MT, Greig NH. Neuroinflammation as a Factor of Neurodegenerative Disease: Thalidomide Analogs as Treatments. Front Cell Dev Biol. 2019 ;7:313

86. Oliveira MCB, de Brito MH, Simabukuro MM. Central Nervous System Demyelination Associated With Immune Checkpoint Inhibitors: Review of the Literature. Front Neurol. 2020 Dec 11;11:538695. doi: 10.3389/fneur.2020.538695.

87. Berraondo-P. Mechansism of action for different checkpoint inhibitors. HemaSphere 2019; 3(S2): 28-30

88. Das R, Bar N, Ferreira M, Newman AM, Zhang L, Bailur JK, Bacchiocchi A, Kluger H, Wei W, Halaban R, Sznol M, Dhodapkar MV, Dhodapkar KM. Early B cell changes predict autoimmunity following combination immune checkpoint blockade. J Clin Invest. 2018; 128:715-720.

89. Arnaud L, Lebrun-Vignes B, Salem JE. Checkpoint inhibitor-associated immune arthritis. Ann Rheum Dis. 2019;78:e68

90. Ghosh N, Tiongson MD, Stewart C, Chan KK, Jivanelli B, Cappelli L, Bass AR. Checkpoint Inhibitor-Associated Arthritis: A Systematic Review of Case Reports and Case Series. J Clin Rheumatol.2020. doi:10.1097/ RHU.0000000000001370

91. Oke AR, Wheater M, Karydis I, Wallis D. Successful use of adalimumab in immune checkpoint inhibitor-associated inflammatory arthritis. Rheumatol Adv Pract. 2018 Jan 30;2:rky001

92. Sengul Samanci N, Ozan T, Çelik E, Demirelli FH. Optic neuritis related to atezolizumab treatment in a patient with metastatic non-small-cell lung cancer. JCO Oncol Pract. (2020) 16:96–98

93. Takemura S, Klimiuk PA, Braun A, Goronzy JJ, Weyand CM. T cell activation in rheumatoid synovium is B cell dependent. J Immunol. 2001;167:4710-8

94. Corsiero E, Nerviani A, Bombardieri M, Pitzalis C. Ectopic Lymphoid Structures: Powerhouse of Autoimmunity. Front Immunol. 2016;7:430.

95.Magliozzi R, Howell O, Vora A, Serafini B, Nicholas R, Puopolo M, Reynolds R, Aloisi F. Meningeal B-cell follicles in secondary progressive multiple sclerosis associate with early onset of disease and severe cortical pathology. Brain. 2007; 130:1089-1104.

96. Pryce G, Baker D. Oligoclonal bands in multiple sclerosis; Functional significance and therapeutic implications. Does the specificity matter? Mult Scler Relat Disord. 2018;25:131-137.

97. Canete JD, Celis R, Moll C, Izquierdo E, Marsal S, Sanmarti R, et al. Clinical significance of synovial lymphoid neogenesis and its reversal after anti-tumour necrosis factor alpha therapy in rheumatoid arthritis. Ann Rheum Dis. 2009; 68:751–756.

98. Salinas GF, De Rycke L, Barendregt B, Paramarta JE, Hreggvidsdottir H, Cantaert T, van der Burg M, Tak PP, Baeten D.Anti-TNF treatment blocks the induction of T cell-dependent humoral responses. Ann Rheum Dis. 2013; 72:1037-1943.

99. Růžičková Š, Cimburek Z, Jarošová K, Forejtová Š, Vencovský J.Plasma cells as a marker predicting the outcome of anti-TNF therapy. Čes. Revmatol. 2007; 15: 179-184.

100. Fresegna D, Bullitta S, Musella A, Rizzo FR, De Vito F, Guadalupi L, Caioli S, Balletta S, Sanna K, Dolcetti E, Vanni V, Bruno A, Buttari F, Stampanoni Bassi M, Mandolesi G, Centonze D, Gentile A. Re-Examining the Role of TNF in MS Pathogenesis and Therapy. Cells. 2020; 9:2290

101. O'Connell J, Porter J, Kroeplien B, Norman T, Rapecki S, Davis R, McMillan D, Arakaki T, Burgin A, Fox Iii D, Ceska T, Lecomte F, Maloney A, Vugler A, Carrington B, Cossins BP, Bourne T, Lawson A. Small molecules that inhibit TNF signalling by stabilising an asymmetric form of the trimer. Nat Commun. 2019;10:5795.

102. Probert L. TNF and its receptors in the CNS: The essential, the desirable and the deleterious effects. Neuroscience. 2015;302:2-22.

Figure legends

Figure 1. Potential difference between anti-TNF therapy in arthritis and multiple sclerosis. Tumour necrosis factor inhibiting agents generate peripheral pathogenic memory B cells that can activate T cells and enter tissues to cause disease. Some agents fail to enter the central nervous system and therefore do not stop the development of blood brain barrier dysfunction and the formation of B cell follicles that develop due to differentiation of memory B cells or via growth factor support of the plasma cell niche. Cytokines and locally-produced antibodies stimulate the innate and adaptive immune systems to induce tissue damage. In arthritis these agents penetrate the tissue and halt the damaging immune responses. Created with Biorender.com

Figure 1: