Viewpoint on anifrolumab in patients with systemic lupus erythematosus and a high unmet need in clinical practice

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ABSTRACT
Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease characterised by unpredictable flares. Many patients with SLE are unable to achieve the recommended treatment goal of remission or the intermediate, yet still clinically beneficial, goal of Lupus Low Disease Activity State (LLDAS) with standard of care (SoC) treatments. LLDAS is an emerging treat-to-target goal in SLE with the aim of reducing organ damage and mortality. A high unmet need remains in SLE and mainstay glucocorticoid treatment is associated with unacceptable toxicity. The recently approved type I interferon receptor antagonist anifrolumab is a new treatment option for this historically underserved patient population. In phase 3 trials, a higher percentage of patients on anifrolumab achieved remission, as defined by the Definition Of Remission In SLE (DORIS), and LLDAS compared with placebo. Real-world clinical experience with anifrolumab use is still limited. Until real-world study results and updated treatment guidelines are available, personal expert clinical experience supported by data may inform clinical decision-making. This viewpoint article discusses four example patient types that could be considered for anifrolumab treatment based on (1) high-risk features early in the disease course, (2) inability to achieve and (3) maintain at least LLDAS, or (4) a desire to reduce or stop SoC. These patients with high unmet need may benefit from the addition of anifrolumab to SoC to achieve or maintain the therapeutic goals of LLDAS or DORIS remission.

INTRODUCTION
Systemic lupus erythematosus (SLE) is a chronic, heterogeneous autoimmune disease with an unpredictable course. It is estimated that as many as 5 million people worldwide have some form of lupus, with approximately 70% of cases having systemic organ involvement. SLE is challenging to diagnose and treat, owing mainly to the complexity of clinical symptoms and relapsing-remitting nature of the disease.

Clinical manifestations can impact many organs and cause a variety of symptoms including fatigue, joint pain, muscle aches and cognitive impairment leading to poor quality of life (QoL). Approximately 30–50% of patients with SLE develop permanent organ damage within 5 years of diagnosis, which can be attributed to disease flares or treatments such as glucocorticoids (GCs) that cause long-term toxicity and increase mortality risk. Therefore, a high unmet need remains for patients with SLE.

Standard of care (SoC) for SLE consists of broad immunosuppressants (IS) and GCs, which are the mainstay of flare management; however, GCs are associated with an increased risk of organ damage, even with lower doses. Serious complications associated with chronic GC use include osteoporotic fractures, cardiovascular damage and an increased risk of infections which contribute to disease accrual. Furthermore, up to one-third of patients with active SLE respond insufficiently to GC treatment, and multiple mechanisms for GC resistance have been described. However, GCs are still extensively used in SLE management, and GC tapering regimens are poorly defined. If GC dose reduction has been achieved, maintenance of that dose, or even GC discontinuation if clinically feasible, is essential. Therefore, providing disease control for patients with SLE without increasing their lifetime GC burden is an important treatment goal.

Biological drugs, such as belimumab and anifrolumab, are also available for the treatment of SLE. Treatment guidelines include guidance on use of belimumab but do not yet include the more recently approved anifrolumab.

The current treatment recommendation for SLE aims for remission of disease symptoms and signs, prevention of damage accrual and improvement of QoL while using the lowest GC dose possible. Multiple definitions of remission have been used in SLE studies, with varying attainability. Currently, the
Definition Of Remission In SLE (DORIS), developed by the DORIS taskforce, is the widely adopted remission definition for SLE. Complete remission is the ultimate treatment goal in SLE, and it is achievable but infrequent. Lupus Low Disease Activity State (LLDAS) is a composite disease measure that includes disease activity and treatment-related domains and is an emerging treatment goal for SLE. LLDAS is a tangible target state associated with a reduction in disease flares and damage accrual, as well as improvement in patient-reported measures such as health-related QoL. About 25% of patients with SLE are unable to achieve LLDAS while receiving SoC alone, and not ever achieving LLDAS is associated with worse QoL, suggesting that some patients only on SoC alone have inadequate disease control and poor outcomes.

Anifrolumab in SLE

Targeted biological therapies provide a new therapeutic option for patients with SLE. While the aetiology of SLE is not entirely understood, activation of type I interferon (IFN) is a key part of SLE immunopathogenesis, and the majority of patients with SLE have overexpression of type I IFN-induced genes. Anifrolumab is a fully human monoclonal antibody specifically targeting the type I IFN receptor alpha 1 subunit, thereby blocking all type-I IFN signalling, which is a key factor of immune dysregulation and inflammation in SLE. Based on results from the phase 2b MUSE and phase 3 TULIP-1 and TULIP-2 trials anifrolumab was approved by the US Food and Drug Administration (FDA) for the treatment of adult patients with moderate to severe SLE who are receiving standard therapy. Subsequently, it was also approved in Canada, Australia, and by the Pharmaceuticals and Medical Devices Agency in Japan for the treatment of adult patients with SLE who show insufficient response to currently available treatment, also by the European Medicines Agency (EMA) for the treatment of adult patients with moderate to severe active autoantibody-positive SLE despite standard therapy.

The long-term safety and tolerability of anifrolumab was investigated in a phase 3 placebo-controlled long-term extension of the TULIP trials (TULIP-LTE). During this 4-year period, anifrolumab treatment was well tolerated and had an acceptable safety profile. Viral infections such as herpes zoster (HZ) and COVID-19 were more prevalent in patients treated with anifrolumab compared with placebo; however, the risk of HZ with anifrolumab was higher in the first year of treatment rather than a long-term treatment concern, and there were no COVID-19–related adverse events in fully vaccinated patients (although post-vaccine exposure was limited). The TULIP-LTE study also showed that patients receiving anifrolumab had maintained reductions in disease activity and GC usage. Furthermore, in a post hoc analysis of the TULIP-LTE study, treatment with anifrolumab was associated with more frequent LLDAS achievement and more cumulative time in LLDAS.

Patient populations with SLE and a high unmet need

This opinion piece, based on recent clinical trial data and personal clinical experience, will provide more information to support physicians in identifying patients who may particularly benefit from the addition of anifrolumab to SoC in the absence of updated guidelines. SLE treatment guidelines have not been updated since anifrolumab was first approved, and although anifrolumab is approved for adult patients with moderate to severe SLE who are receiving standard therapy, there is no consensus on which patients should be considered for anifrolumab in clinical practice. Data from the MUSE and TULIP trials have provided valuable insights into the positive benefit–risk profile of anifrolumab across a wide range of clinically important global and organ-specific measures of disease activity in adult patients with moderate to severe SLE receiving standard therapy. Of note, anifrolumab demonstrates efficacy across a broad range of organ manifestations. As the MUSE and TULIP trials demonstrated the safety and efficacy of anifrolumab treatment in different subpopulations of patients with SLE, including those with high unmet need with SoC, hypotheses may be generated to define the types of patients in regular clinical practice who may benefit the most from anifrolumab treatment (figure 1).

Patients with moderate to severe SLE and high-risk features early in the disease course

Early age of onset, presence of anti–double-stranded DNA (anti-dsDNA) autoantibodies, non-Caucasian race, presence of antiphospholipid antibodies and higher disease severity at diagnosis are generally associated with a disease course with a higher frequency of organ and system involvement, treatment emergent adverse events (AEs) due to more aggressive treatment, and higher disease- and all-cause mortality. Patients with moderate or severe SLE at diagnosis have higher risk of cardiovascular disease, burden of disease flares and all-cause mortality compared with patients with mild disease at diagnosis. Lupus nephritis (LN) is a severe manifestation of SLE that occurs in ~50% of patients; it is usually diagnosed early in the disease course of SLE and can be present at diagnosis. The development of LN is associated with high-risk factors (eg, young age, non-Caucasian race), and is itself a high-risk feature for increased mortality.

Hydroxychloroquine (HCQ) is recommended as part of induction and subsequent therapy for all patients with SLE, unless contraindicated, given its protective effects of flare reduction and against organ damage accrual, although concerns over retinal toxicity have led to daily doses ≥5 mg/kg not being recommended. IS, including mycophenolate mofetil (MMF) or intravenous cyclophosphamide (IVCY), are also recommended as part of induction therapy for patients presenting with...
organ-threatening disease, including with LN.\(^6\) However, both MMF, which has teratogenic potential, and IVCY, which has gonadotoxic effects, need to be discontinued or used with caution in pregnant women or women/men of fertile age, respectively.\(^6\) Thus, there is still an urgent need for other effective agents for patients with severe, high-risk SLE, in which life-threatening or organ-threatening features are present (population 1, figure 1).\(^9\)

Belimumab is currently the only FDA- and EMA-approved biological therapy for adult patients with active LN receiving standard therapy.\(^30\)\(^31\) Although more data are needed for the use of anifrolumab in renal SLE manifestations, recent evidence from the phase 2 TULIP-LN study has shown that an intensified anifrolumab dose reached clinical efficacy for patients with LN\(^32\); a phase 3 clinical trial is ongoing.\(^33\)

Anifrolumab has proven efficacious in adult patients across multiple SLE subgroups with moderate to severe disease including those who have characteristics indicative of a worse overall prognosis and in patients with shorter disease duration (time since diagnosis). In TULIP-1 and TULIP-2, British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA) response rates at Week 52 of anifrolumab treatment were similar regardless of age of onset (paediatric vs adult); anti-dsDNA (positivity or negativity); race (White, African American and Asian); and disease severity at diagnosis (moderate or severe).\(^34\)\(^35\) As assessed by BICLA response, post hoc analyses of TULIP-1 and TULIP-2 demonstrated that anifrolumab was efficacious after 52 weeks of treatment in patients with established (disease duration >2 years) or recent-onset (disease duration ≤2 years) disease.\(^36\) Given that anifrolumab treatment facilitated more GC tapering while maintaining disease control compared with placebo in TULIP trials,\(^37\) and earlier disease control can prevent damage accrual,\(^3\) anifrolumab treatment within the first year after diagnosis, for patients with high-risk features, could improve disease course and reduce the risk of morbidity and mortality.

Patients with moderate to severe SLE who are unable to achieve at least LLDAS with existing SoC treatments

As treat-to-target (T2T) approaches have become part of the SoC in other chronic conditions and have transformed patient outcomes, the potential benefit of using T2T approaches in SLE management has gained interest.\(^20\)\(^38\) Though LLDAS is considered to be an appropriate treatment goal for patients with SLE and easier to achieve than remission,\(^6\) achieving LLDAS with SoC therapy remains a challenge for patients with moderate to severe active SLE.\(^39\) Patients who are unable to achieve at least LLDAS with SoC have poor outcomes and an undesirable disease state that requires treatment escalation and better therapeutic approaches (population 2, figure 1).\(^20\)

In a post hoc analysis of the pooled TULIP-1/TULIP-2 trials, 15.5% of anifrolumab-treated patients (300 mg every 4 weeks (Q4W)) achieved DORIS remission at Week 52, compared with 7.6% of patients treated with placebo (odds ratio (OR) (95% confidence interval (CI)): 2.2
For patients who attain LLDAS and experience a flare, anifrolumab could be an alternative therapeutic approach as a treatment strategy to resolve flares, over the option of short-term increase in GC dose, due to its rapid onset of action and sustained efficacy while enabling a reduction in GC use over the long term. Furthermore, more proactive approaches with earlier anifrolumab use may benefit patients who are unable to sustain LLDDAS by reducing the risk of flares. As evidence shows that early biological use leads to better outcomes in SLE management and in other similar conditions such as rheumatoid arthritis, patients may benefit from earlier anifrolumab treatment and could maintain LLDDAS.

Patients with moderate to severe SLE who maintain LLDDAS and wish to further reduce or stop GC

Sustained LLDDAS or DORIS remission was reported as protective against late disease flares and accrual of additional organ damage. A higher flare rate later in the disease course is also observed in patients receiving higher GC doses, with tapering to ≤7.5 and ≤5 mg daily of prednisone or equivalent being an integral part of the LLDDAS and DORIS definitions, respectively. IS are recommended for patients who do not respond to induction therapy (including HCQ with or without GCs) and for patients who are unable to reduce GC doses to an acceptable level for chronic use. However, use of IS agents such as methotrexate and MMF is limited based on the predominant disease manifestations, the patient’s age and childbearing potential, and safety and/or tolerability concerns (mainly liver, gastrointestinal and haematological AEs).

IS tapering or discontinuation may thus be desirable for many patients, but use of these strategies is limited as they are not part of the current European Alliance of Associations for Rheumatology treatment recommendations. Therefore, successful SLE management requires additional therapeutic approaches that maintain LLDDAS and/or remission and enable tapering or stopping GC (figure 1). Given the well-tolerated and acceptable long-term safety profile, and the positive impacts on GC tapering and attainment of DORIS remission, anifrolumab may be a treatment option to achieve these therapeutic goals.

In a pooled post hoc analysis of TULIP-1/TULIP-2, anifrolumab treatment reduced annualized flare rates and extended time spent flare free compared with placebo while permitting GC tapering. Specifically, among patients receiving ≥10 mg/day GCs at baseline, more patients receiving anifrolumab compared with placebo achieved sustained GC taper to ≤7.5 mg/day (96 of 190 (50.5%) vs 59 of 185 (31.8%)). Similarly, in a recent TULIP post hoc analysis, greater GC dose reductions from Week 20 to Week 52 were observed in anifrolumab-treated patients who were receiving ≥10 mg/day GCs at baseline compared with those on placebo (least squares mean difference (95% CI), Week 20: −12.72 mg/day (−22.34 to −3.10), P=0.010; Week 52: −14.80 mg/day (−27.17 to −2.42), P=0.019). Furthermore, in patients receiving GCs...
>7.5 mg day GCs at baseline, the anifrolumab group spent longer duration receiving a ≤7.5 mg/day dose by Week 52 compared with placebo (mean standard deviation (SD) duration: 161.4 days (119.5) vs. 126.1 days (119.6)).

In the TULIP-LTE study, sustained improvements in disease activity and reductions in GC use continued in patients treated with anifrolumab for up to 4 years, even though GC tapering was not required by the TULIP-LTE protocol. A lower proportion of patients treated with anifrolumab received mean >7.5 mg/day GCs over the 4 years of the TULIP trial and LTE study, compared with placebo. At Year 4, the end of the LTE study, fewer patients in the anifrolumab group were receiving >7.5 mg/day GCs compared with the placebo group (9.9% vs. 29.3%, respectively), and a larger percentage were GC free (36.4% vs. 26.8%, respectively). Taken together, these data suggest that anifrolumab treatment may enable patients to meet a key treatment goal of reducing GC usage while maintaining disease control.

CONCLUSIONS

In summary, although anifrolumab has demonstrated benefit for a broad population of adult patients with moderate to severe SLE who are receiving standard therapy, we have proposed patient populations with a high unmet need that may particularly benefit from anifrolumab treatment, including those who have inadequate disease control while on SoC or those who are unable to tolerate their standard treatment. We acknowledge currently limited data are available to demonstrate effectiveness and safety in the real-world setting. Nonetheless, robust supporting evidence from clinical trials indicates that many of the current treatment goals can be achieved with anifrolumab. The positive anifrolumab benefit–risk profile and GC tapering continued to be observed in the placebo-controlled TULIP-LTE study which was designed to mimic real-world clinical practice without an enforced GC taper.

While GC use and toxicity remain a challenge in current management of SLE, anifrolumab is another biological treatment option to reduce disease activity and minimise GC burden in patients with SLE. Ongoing real-world evidence is emerging for anifrolumab as a treatment option in adult patients with moderate to severe SLE and will clarify patient populations most likely to attain the best outcome with treatment.

Acknowledgements The author sincerely thanks Dr. Hussein Al-Mossawi for helpful discussion. The work of the author was supported by AstraZeneca, but AstraZeneca played no role in data collection or analysis. Medical writing support was provided by Kelly Hunter, PhD and Tamara Finn, PhD of JK Associates, Inc. part of Fishawack Health.

Contributors YT conceived and designed the article, YT analysed and interpreted the intellectual content, and was involved in the development, review and final approval of the article. YT is the author acting as the guarantor.

Funding This article was supported by AstraZeneca.

Disclaimer The funder had a role in the concept design, interpretation of the intellectual content, development of the article and final approval to submit the article for publication. The funder had no role in data collection or analysis.

Competing interests YT has received grant/research support from Chugai, Eisai, Mitsubishi-Tanabe and Taiso; received speaking fees and/or honoraria from AbbVie, AstraZeneca, Boehringer-Ingelheim, Bristol Myers Squibb, Chugai, Eisai, Eli Lilly, Gilead, GaoxSmithKline, Pfizer, Taiho and Taisho.

Ethics approval Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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