Rheumatology, 2024, **00**, 1–12
https://doi.org/10.1093/rheumatology/keae178
Advance access publication 14 March 2024
Review

Review

Can complement activation be the missing link in antiphospholipid syndrome?

Veronica Venturelli[1,2,3], Beatrice Maranini[1], Ibrahim Tohidi-Esfahani[4,5], David A. Isenberg [2], Hannah Cohen [3,6], Maria Efthymiou[3,6,*]

[1]Rheumatology Unit, Department of Medical Sciences, Università degli Studi di Ferrara, Azienda, Ospedaliero-Universitaria S. Anna, Cona, Italy
[2]Centre for Rheumatology, Department of Medicine, University College London, London, UK
[3]Department of Haematology, Cancer Institute, University College London, London, UK
[4]Haematology Department, Concord Repatriation General Hospital, Sydney, Australia
[5]Faculty of Medicine and Health, University of Sydney, Sydney, Australia
[6]Department of Haematology, University College London Hospitals NHS Foundation Trust, London, UK

*Correspondence to: Maria Efthymiou, Department of Haematology, Cancer Institute, University College of London, Second Floor, Laboratory 207, Paul O'Gorman Building, 72 Huntley Street, London WC1E 6BT, UK. E-mail: m.efthymiou@ucl.ac.uk

Abstract

APS is an autoimmune disorder with life-threatening complications that, despite therapeutic advantages, remains associated with thrombotic recurrences and treatment failure. The role of complement activation in APS pathogenesis is increasingly recognized, specifically in obstetric APS. However, its exact role in thrombotic APS and on the severity of the disease is not yet fully elucidated. Further mechanistic studies are needed to delineate the role of complement activation in the various APS clinical manifestations with aim to identify novel markers of disease severity, together with clinical trials to evaluate the efficacy of complement inhibition in APS. This could ultimately improve risk stratification in APS, patient-tailored targeted therapy with complement inhibition identified as an adjunctive treatment. This article reviews current findings and challenges about complement activation in APS, discusses the potential role of platelet-mediated complement activation in this setting and provides an overview of clinical implications and current therapeutics.

Keywords: antiphospholipid syndrome, antiphospholipid antibodies, complement, coagulation, thrombosis, pregnancy outcomes.

Rheumatology key messages

- Complement activation is key in APS pathophysiology.
- Increased complement activation is observed in most severe APS clinical manifestations (recurrent thrombosis, catastrophic APS).
- Complement inhibition could be an adjunctive treatment to current therapeutic strategies for some APS patients.

Introduction

APS is an autoimmune disease with life-threatening complications that, despite therapeutic advances, continues to cause significant mortality and morbidity [1, 2]. It is characterized by thrombotic events (TE) occurring in venous, arterial and small vessels, and/or obstetric morbidity, with concomitant persistent positivity of at least one of three aPL, LA, anti-β2-glycoprotein I (aβ2GPI) and aCL [3]. APS can be diagnosed in the context of other autoimmune diseases, notably SLE, or it can occur on its own (primary APS, PAPS) [4]. Importantly, the presence of aPL alone is associated with an increased risk of TE, which increases with the number of positive aPL, and with higher titre [5].

Long-term anticoagulation with vitamin K antagonists is the mainstay of treatment for APS [6], derived from the observed high thrombotic recurrence rates (25–44%) [1, 7, 8]. Treatment failures and anticoagulant-refractory cases still occur, with the risk of recurrent TE particularly high in APS patients with arterial thrombosis (ATE) (over 20%) compared with those with venous thrombosis (VTE; 5.4%), despite therapeutic anticoagulation [9]. This finding suggests that additional mechanisms not affected by anticoagulation may play a decisive role in the observed hypercoagulability in APS.

Inhibition of the natural anticoagulant and fibrinolytic systems [10–13], activation of platelets [14], monocytes [15] and endothelial cells [16], neutrophils and neutrophil extracellular traps (NETs) [17], inflammation [18], and complement activation [19, 20] have been proposed as key components in APS pathophysiology. The exact mechanisms

Received: 20 December 2023. **Accepted:** 10 March 2024

and contribution of each in the heterogeneous clinical APS manifestations are still unclear.

Based on the documented crosstalk between complement and coagulation pathways [21], activation of complement could be an adjunctive mechanism that could explain the pathogenic effects of aPL and the frequent failure of anticoagulation treatment.

Complement is an enzymatic cascade of circulating and cell-bound proteins, which promotes inflammation and defence against microbes. It encompasses three pathways activated by different triggers: antigen–antibody complexes (classical pathway), pattern-recognition molecules binding to pathogens (lectin pathway), microorganism-associated molecular pattern and the spontaneous hydrolysis of C3 (alternative pathway) [22, 23]. The pathways converge at the formation of C3 and C5 convertases. C3 is cleaved into C3b and C3a, while C5 is cleaved into C5a and C5b leading to the terminal complement pathway. C5b initiates the assembly of the membrane attack complex (MAC, C5b-9), which causes cellular lysis, while C3a and C5a induce the release of proinflammatory cytokines (Fig. 1) [24]. Complement pathways are very tightly controlled by various mechanisms either in fluid phase or membrane bound, with failure of these leading to complement-mediated direct cellular injury and thrombosis.

The role of complement as a key element in the pathogenesis of thrombosis has been well recognized in thrombotic disorders such as paroxysmal nocturnal haemoglobinuria (PNH) and atypical haemolytic uraemic syndrome (aHUS), where treatment with complement inhibitors (e.g. eculizumab) has significantly reduced the rate of TE [8].

The role of complement in the pathogenesis of APS is increasingly becoming more widely recognized. Its involvement in aPL-mediated thrombosis has been shown by various studies and its critical role was established in aPL-mediated pregnancy complications outlined below.

Complement activation in APS

Levels of various components derived from complement activation have been consistently found elevated in the serum of APS patients or aPL carriers. Studies in APS patients found evidence of complement activation via both the classical pathway and alternative pathway [25–27].

Thus, patients with aPL-mediated stroke exhibit significantly higher C5b-9 levels than those without aPL [28]. Elevated levels of C5b-9 and C5a are reported in catastrophic APS (CAPS) during the acute and subclinical phases [29, 30]. Fragment Bb, C3a/C3a-desArg (the inactivated form of C3a) and C4a are significantly higher in PAPS patients and in aPL carriers compared with healthy controls [25, 27]. Since elevated complement components are also detected in patients without TE, it is reasonable to think that complement activation is not a consequence of thrombosis or adverse pregnancy outcomes (APOs), but a phenomenon induced by the presence of aPL. Interestingly, Breen *et al.* [27] did not find any significant differences in complement activation (elevated Bb and C3a-desArg levels) between different clinical phenotypes of aPL-positive patients (aPL-carriers, thrombotic and obstetric APS). This was despite increased Bb and C3a-desArg levels being associated with aPL profiles such as double/triple aPL or persistent LA positivity, regarded as the most likely to be linked to thrombosis. It must be acknowledged that not all patients with high-risk aPL profiles develop APS-related events. Thus, when aPL are detected in a patient without any previous TE, an aPL profile alone is of uncertain predictive value for the subsequent development of thrombosis in the

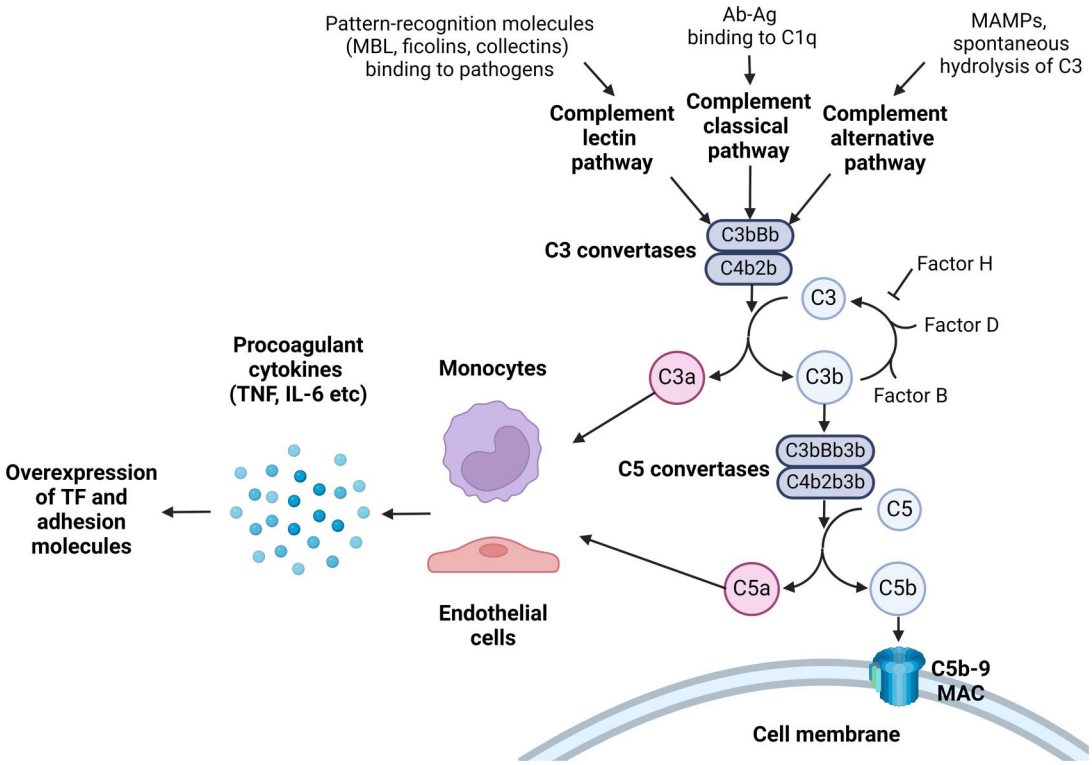

Figure 1. The complement cascade. Created with BioRender.com. Ab: antibody; Ag: antigen; MAC: membrane attack complex; MAMPs: microorganism-associated molecular patterns; MBL: mannose-binding lectin; TF: tissue factor

majority of cases. However, Pengo *et al.* [31] identified that triple aPL positive profile was associated with a cumulative incidence of TE that increased with time (9.8% after 2 years, 27.3% after 5 years, and 37.1% after 10 years). A more recent study observed significantly higher levels of C5b-9 in patients with high titres and IgG aPL (both well-documented markers of disease severity), suggesting that C5b-9 levels could also be a biomarker in aPL-positive patients [32].

However, serum levels of complement fragments can be often misleading (Fig. 2), especially in patients with concomitant SLE, which can cause hypocomplementemia, or in those taking certain anticoagulants. Grosso *et al.* [33] suggested that warfarin could cause a reduction in C4b-binding protein, which was associated with reduced complement components levels, while other authors [34, 35] reported reduced levels of complement components during treatment with unfractionated and low molecular weight heparin *in vivo* and *in vitro*. Given these limitations, functional assays such as the modified Ham (mHam) assay can provide a more direct and reliable measurement of complement activity (Fig. 2). It measures the degree of non-viable PIGA^{null} cells, which are susceptible to complement-induced killing since they lack two regulatory proteins, CD55 and CD59 [36, 37], after incubation with patient serum. The results of the mHam assay represent the final effect of C5b-9 complex formation. Hence, it cannot identify the specific pathway activated, but can detect overall function of complement activation [38]. Chaturvedi *et al.* [39] found that almost 86% of patients with CAPS had a positive mHam result, while positivity was only 35.6% in APS patients and significantly lower in SLE patients (6.8%). Analysis of C5b-9 deposition on PIGA^{null} cells following addition of APS patient serum and administration of an anti-C5 antibody and a factor D inhibitor, revealed that complement-induced cell-killing observed with the mHam assay was mostly due to activation of the classical pathway.

Another functional method to estimate complement activation is the detection of the biologically inactive complement components bound to cell surfaces [40]. Deposition of C4d on erythrocytes (EC4d) and platelets (PC4d) has been considered as a hallmark of the *in vivo* activation of the complement cascade in APS patients. A significantly higher percentage of EC4d and PC4d was noted in PAPS and SLE-associated APS when compared with controls (including healthy individuals, aPLs carriers, aPL-negative patients with previous thrombosis, patients with a diagnosis of immune thrombocytopenic purpura). Patients with SLE without APS also exhibited increased EC4d and PC4d, but less significantly than APS patients [41]. Consistent with this observation, Svenungsson *et al.* [42] showed PC4d to be more prevalent in aPL-positive SLE patients than in those without aPL.

Complement activation and various aPL profiles

aPL have variable ability to fix and activate the complement cascade [43]. In a study by Chaturvedi *et al.* [39], almost 44% of 32 patients only positive for aβ2GPI had a positive mHam assay, while only 26% of those positive for only aCL ($P = 0.154$) were mHam positive. As acknowledged by the authors, the small size of the groups may have obscured detection of a statistically significant difference. In a separate study, significantly more intense complement consumption was observed in patients with thrombotic APS with circulating immune complexes of IgG/IgM aβ2GPI–β2GPI (β2-CIC) compared with patients without β2-CIC [44].

A significant positive correlation between C4d deposition and titre of some aPL isotypes was also reported by Lonati

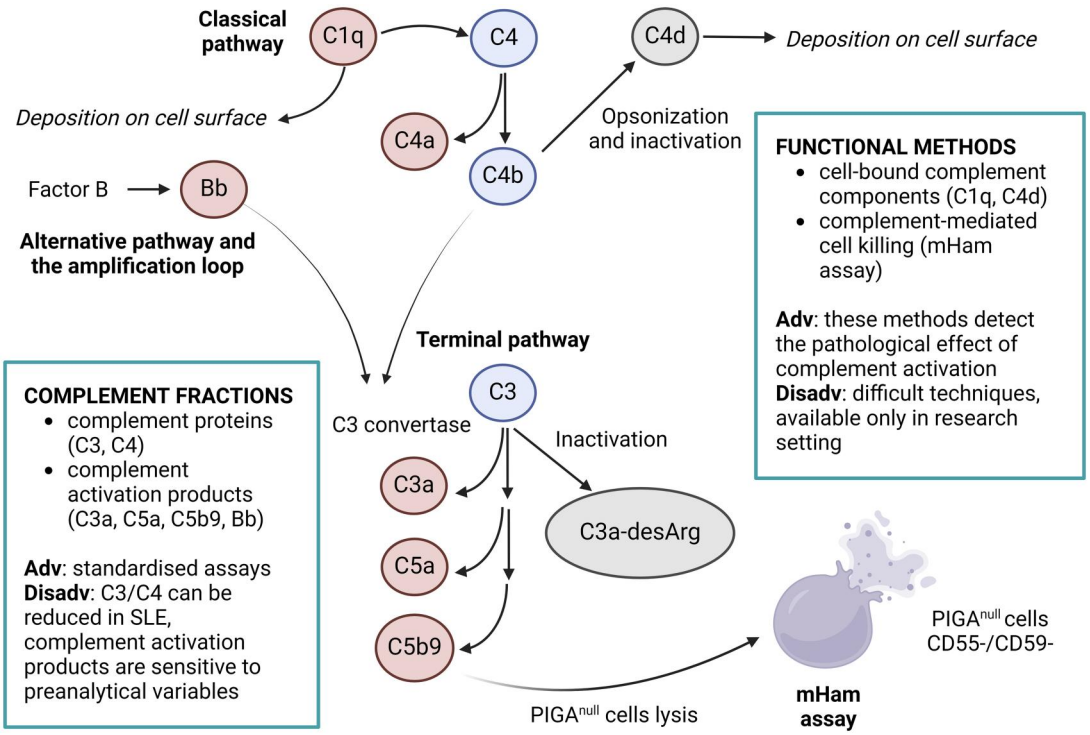

Figure 2. Methods to measure complement activation. Created with BioRender.com. Adv: advantages; Disadv: disadvantages; mHam: modified Ham

et al. [41]. More specifically, PC4d correlated significantly with IgG aβ2GPI and IgG/IgM aCL, while EC4d with IgG/IgM aβ2GPI and IgG/IgM aCL, with the strongest correlation being with IgG aCL in both cases ($r = 0.4537$, $P < 0.0001$, with PC4d and $r = 0.4805$, $P < 0.0001$, with EC4d). These findings support the notion that aPL can activate complement leading to deposition of C4d on cells that more importantly appears to increase with higher aPL titres. Zen *et al.* [32] confirmed enhanced complement activation in patients with higher aPL titre and with IgG. Significantly higher levels of C5b-9 were observed in patients with multiple aPL positivity *vs* single positivity, and in patients with IgG aCL/aβ2GPI at high *vs* medium titre. No difference was found when IgM aPL were studied and C5b-9 levels were similar between patients with APS and aPL carriers, suggesting subclinical complement activation, with possible relevance as a basis for prophylactic strategies.

Furthermore, a recent study identified that a subset of patients with APS may be at increased risk for development of CAPS because of the presence of germline variants in genes crucial for complement regulation, present in 60% of CAPS patients, a similar rate to aHUS patients (51.5%), 21.8% thrombotic APS and 23.3% healthy subjects [39]. In addition, an association between multiple aPL positivity and increased levels of complement fragment Bb has also been reported in APS patients [45]. The alternative pathway appears to be the main complement pathway implicated in patients with high-risk aPL profiles [45].

Overall, data indicate that IgG aCL and aβ2GPI can activate the complement cascade in both APS patients and in aPL carriers, without any differences in the degree of activation (i.e. amount of C5b-9 generated). It appears that high levels/titres of aPL are a stronger trigger of complement activation compared with moderate titre.

Coagulation and complement activation interplay

Coagulation and complement activation are interlinked with both pathways able to activate each other through multiple components [46].

Blood clotting results from a complex sequence of events and from the interplay between different cell populations, the exposed subendothelial tissue, the extracellular matrix (ECM), coagulation factors and complement components [47]. Briefly, upon tissue damage, platelets adhere to the exposed collagen on the damaged vessel wall, which leads to their activation. Platelet adhesion starts with interactions between platelets surface receptors and ECM components [48]. Upon adhesion and activation, platelets undergo a conformational change that redistributes the membrane phospholipids, increasing the exposure of phosphatidylserine [49] and chondroitinsulphate, which support complement activation [50]. Activated platelets degranulate, releasing coagulation factors [prothrombin, factor (F) V, FXI, FXIII] [51] and complement components [52]. Secondary haemostasis is initiated with either the tissue factor (TF) pathway or the contact pathway, both merging at production of activated FX (FXa) that subsequently cleaves prothrombin to thrombin. Fibrinogen is then cleaved by thrombin to fibrin resulting in fibrin deposition and strengthening of the initial platelet plug. Both primary and secondary haemostasis occur simultaneously and can be influenced by the activity of complement components [23]. Blood clotting can occur in the absence of vessel injury for instance in the presence of aPL.

Regarding the complement–coagulation interplay, factor H (FH), a complement regulator, modulates some coagulation factors of the intrinsic and common pathways [53]. *In vitro* observations suggest that thrombin generation might also be mediated by MBL (mannose-binding lectin)-associated serine protease 2 (MASP-2), a protease of the lectin pathway, whereas MASP-1 cleaves factor XIII, high-molecular weight kininogen and fibrinogen [54], and initiates the contact pathway of coagulation.

End products of complement activation (C3a, C5a, C5b-9) can induce release of procoagulant and proinflammatory cytokines from endothelial cells and monocytes that lead to overexpression of TF and molecules favouring platelet adhesion and coagulation (Fig. 1) [55, 56].

In aPL-positive individuals, aPL can, by themselves, activate some of the cell populations involved in blood clotting, mainly endothelial cells and platelets [57], and induce monocyte TF expression and FXa release upon TF pathway activation [58, 59].

Interactions between complement and platelets in APS/aPL patients

Several studies demonstrated the effect of complement on different cell types, with induction of TF expression on neutrophils, monocytes and endothelial cells [60, 61], amplification of TF procoagulant activity on monocyte [62] and induction of procoagulant platelets [63, 64]. In this section we will focus on complement–platelet interactions and thrombosis in APS patients.

The relationship between complement, platelets and coagulation is well documented. Wiedmer *et al.* [63] demonstrated that C5b-9 can induce conversion of prothrombin to thrombin on platelets with 10- and 4-fold higher rates compared with controls and to thrombin-induced platelets, respectively. In addition, assembly of C5b-9 on the platelet membrane resulted in a dose-dependent increased binding of FVa and FXa alone with an increased platelet prothrombinase activity [64]. This might be the case in APS but data are limited.

Activation of the classical pathway on platelets has been observed in both APS and SLE patients. Peerschke *et al.* [65] found that serum from both aPL-positive patients (PAPS, aPL-positive without APS, SLE with APS/aPL) and from SLE aPL-negative patients can activate the classical pathway (increased deposition of C1q on heterologous platelets) when compared with healthy controls. Interestingly, serum that exhibited high level of classical pathway activation, regardless of the presence of SLE or APS, demonstrated the ability to activate platelets. Both SLE and aPL positivity may be independently linked to complement activation, leading to *in vitro* platelet activation. The ability of aPL to support complement activation was confirmed by Lood *et al.* [66], who demonstrated that IgG aCL incubation with low-grade activated platelets could amplify platelet activation and support activation of the classical pathway through PC4d deposition on fixed activated platelets.

In PAPS patients, but not in SLE patients without APS, the concomitant presence of low concentration of MASP-2 (due to MASP-2 deposition on platelets and its subsequent consumption) and high levels of activated platelets has been reported [67]. This suggests that activation of the lectin pathway might

be an APS-specific biological feature and that the mechanisms underlying the increased thrombotic risk in SLE with/without APS might differ. Activated platelets demonstrated the ability to trigger MASP-2 through ficolins [54], with MASP-2 activation resulting in the generation of thrombin.

It seems plausible that aPL adhere on the surface of platelets forming immune complexes, recognized by complement components [65]. The subsequent activation of the classical pathway leads to activation of platelets, which further augments activation of complement through the lectin pathway. Apart from aPL, other factors are thought to be also implicated in the deposition of complement components on platelets. Indeed, after *in vitro* incubation of healthy donors' whole blood with a monoclonal antibody against $\alpha\beta$2GPI (MBB2), the median percentage of C4d-positive activated platelets was only 3%. Pathogenic aPL may bind activated platelets more easily than resting ones. This concept was supported by the observation that following addition of a thrombin receptor activating peptide, MBB2 was found on a significantly greater proportion of platelets (7.5%) compared with <1% observed before addition of the agonist ($P = 0.002$) [41].

Recent data showed that platelet activation can be also indirectly mediated by complement through MAC-mediated haemolysis (Fig. 3) [68]. Conversely, it has been demonstrated that platelets exposed to certain agonists (i.e. thrombin or arachidonic acid) or shear stress *in vitro* and some components of the coagulation cascade (FXI, FIX, FX, thrombin, plasmin) can also activate complement [69, 70].

Other factors activating the complement cascade in APS

Apart from aPL, anti-NETs and anti-FH antibodies also can activate the complement pathway in APS. aPL can trigger neutrophils to extrude NETs (structures containing enzymes, histones and DNA [71]) resulting in high circulating levels of NETs in APS patients, providing increased surfaces for complement activation [72, 73]. IgM anti-NET, found elevated in PAPS patients [74], have been associated with complement activation. It has been hypothesized that IgM anti-NET antibodies interact with complement components on the NET surface leading to complement activation [75].

Autoantibodies interfering with the function of complement regulators can also lead to the activation of the terminal pathway. For instance, levels of FH detected in PAPS, were significantly lower compared with patients without a history of aPL-related thrombosis [76, 77], probably as a consequence of the presence of anti-FH antibodies [78] or of FH mutations [76].

Clinical implications

Obstetric APS

The pathogenic relationship between aPL and complement activation in pregnancy has been established in murine models, where complement inhibition has been shown to prevent APOs [79, 80]. Biopsies of human placental tissue collected from aPL-positive women revealed deposits of C4d, but not C3d [81]. The presence of CD55, a regulatory protein expressed by syncytiotrophoblasts, may explain the absence of C3 split products, as CD55 interacts with C4b, interfering with the subsequent steps of the complement cascade [82].

In the EUROAPS (European Registry on Obstetric Antiphospholipid Syndrome) Registry, 223 (21.3%) women had hypocomplementemia (C3 and/or C4) [83, 84]. Women with APS and low complement levels are more likely to experience hypertensive disorders during pregnancy (regarded as a risk factor for pregnancy complications) [85], pregnancy loss, shorter duration of pregnancy and higher frequency of late fetal growth restriction [84]. Nalli *et al.* [86] reported

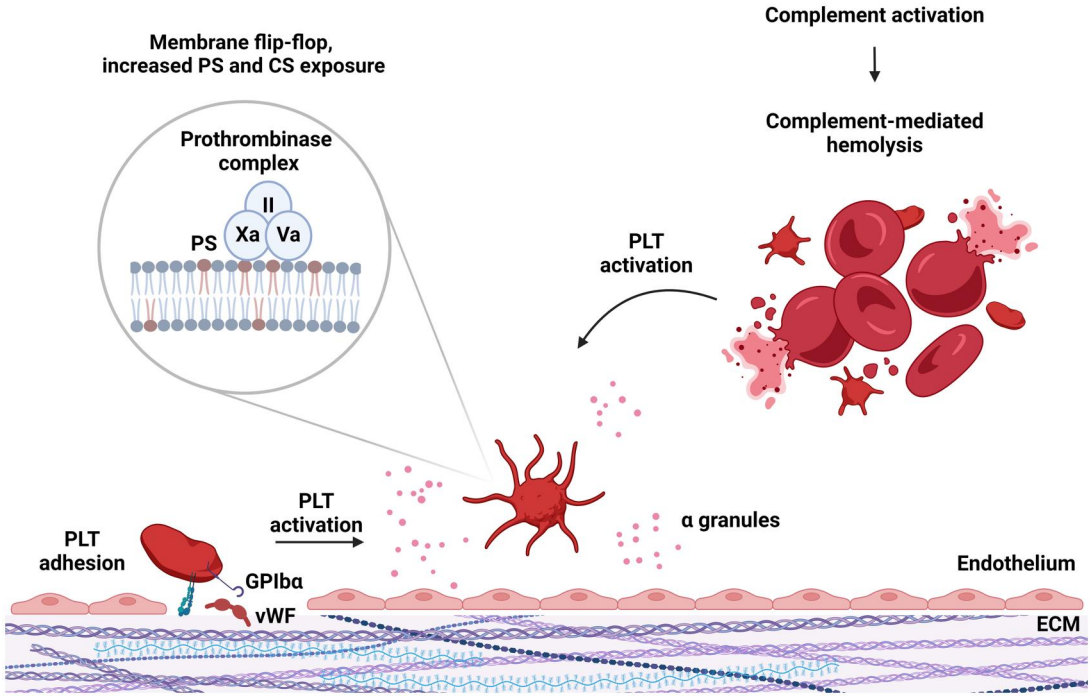

Figure 3. Platelet activation. Created with BioRender.com. CS: chondroitin sulphate; ECM: extracellular matrix; PLT: platelet; vWF: von Willebrand Factor; PS: phosphatidylserine; GPIbα: glycoprotein Ibα

significantly lower pre-conception plasma C3 and C4 in aPL-positive patients who more commonly experienced premature delivery and pregnancy loss, without the differences being linked to the presence of previous APS-related manifestations or aPL profile. However, following subgroup analysis the association remained only for triple aPL-positive women and a higher rate of pregnancy loss. In the PROMISSE (Predictors of pRegnancy Outcome: bioMarkers In antiphospholipid antibody Syndrome and Systemic Lupus Erythematosus) study, Bb and C5b-9 levels at 12–15 weeks of pregnancy were predictive of APOs in women with SLE and/or aPL. For Bb, the association was stronger in aPL-positive patients [odds ratio (OR) = 2.01, $P = 0.013$] than in those without aPL (OR = 1.28, $P = 0.21$), while it was similar when levels of C5b-9 were considered (for aPL-positive patients OR = 1.35, $P = 0.19$; for aPL-negative OR = 1.39, $P = 0.07$). This study suggests that the presence of aPL leads to activation of the alternative pathway, resulting in an increased frequency of obstetric complications [87]. Overall, the evidence supports the role of complement in aPL-mediated obstetric morbidity regardless of SLE.

Thrombotic APS and recurrent thrombosis

The risk of recurrent TE, particularly while on therapeutic anticoagulation, represents a major concern in the management of thrombotic APS, with an annual incidence of 3%, resulting in organ damage, most commonly neurological impairment [7]. A positive mHam assay was reported to be twice as common among patients with recurrent thrombosis compared with those who had experienced a single episode, 66.7% and 33.3%, respectively. In addition, patients who experienced recurrent VTE appear to have persistent complement activity, defined as mHam positivity detected for more than 1 year after the TE [39]. Ruffatti *et al.* [88] showed that plasma levels of C5a and C5b-9 were significantly higher in patients with anticoagulant-refractory APS compared with those without recurrence, further supporting the hypothesis that complement activation is a key component in determining an increased risk of recurrent TE. Another factor found to be associated with VTE recurrence is the presence of anti-FH antibodies, which have been associated with a 2-fold increased risk [78].

Considering that patients with APS and a first ATE on anticoagulation showed a rate of recurrent TE that was four times higher than in those with a first VTE [9], it is reasonable to think that these two clinical situations (APS with initial ATE *vs* with initial VTE) might be to some degree different in their biological features. However, C5a and C5b-9 were found to be similar in PAPS patients with either an initial ATE or VTE [32], while a second study reported significantly lower levels of C5b-9 in patients with PAPS and a previous ATE or VTE [88]. However, the lack of any difference could be due to the small cohorts used in both studies [32, 88].

Consistent with the findings reported above, Peerschke *et al.* [65] did not observe any association with PC4d and ATE in patients with aPL in the absence of other concomitant autoimmune disorders. Conversely, PC4d was significantly associated with ATE in SLE patients regardless of aPL, probably because other SLE-specific factors were a determinant in increasing the risk of ATE [89, 90]. It has been observed that deposition of C4d on platelets led to changes in platelets' phenotype (could aggregate more easily). This observation may provide a biological explanation for the observed association between PC4d and an increased risk of ATE [90]. Furthermore, a synergistic effect on the risk of vascular events in SLE patients has been observed with concomitant C4d deposition on platelets and LA positivity [42].

CAPS

Many authors reported low plasma C3/C4 or elevated C5b-9 when measured during acute CAPS episodes [29, 91], together with high activity of the alternative pathway [29]. More than 85% of CAPS patients exhibited increased complement activity during the acute phase, assessed by the mHam assay [39]. Higher levels of C5a and C5b-9 have been found during the acute phase (ongoing thrombosis) of the disease compared with the subclinical phase in patients with thrombotic, anticoagulant-refractory and CAPS [88]; also during the subclinical phase of CAPS compared with thrombotic APS and healthy controls [30]. Furthermore, a significantly increased frequency of complement gene variants has been reported in CAPS patients (60%), when compared with thrombotic APS (21.8%) and healthy subjects (23.3%), reinforcing an important role for complement in this subset of APS patients [39] (see Table 1 for further details on the studies mentioned). Overall, these data support the importance of complement activation in determining the severity of APS manifestations (such as CAPS), and a potential role for complement inhibition as an adjunctive treatment in APS patients.

Complement inhibition in thrombotic APS, CAPS and obstetric APS

According to the European recommendations for the management of APS [6], complement inhibition should be considered only in patients with CAPS non-responsive to standard therapies, while no recommendation is provided in McMAster RARE-Bestpractises guidelines for CAPS [92]. Analysis of the CAPS registry revealed outcomes from 39 patients treated with eculizumab, of whom 74.4% went into remission without relapse. López-Benjume *et al.* [93] suggested that addition of eculizumab over the standard of care treatments in CAPS patients with symptoms of thrombotic microangiopathy following the administration scheme used in the aHUS could be beneficial [94].

In one case report, eculizumab was used to treat recurrences in thrombotic anticoagulant and immunosuppressive-refractory APS with no recurrent TE for >27 months [95].

Eculizumab has been used in pregnant PNH women with an acceptable safety profile [96]. Gustavsen *et al.* [97] successfully administered it to a pregnant woman with thrombotic APS, based on the estimated high risk of CAPS. The patient did not experience TE in the peri-/postpartum and a fall in complement activity was recorded after the first infusion.

Conclusions and future perspectives

The complement cascade is considered a key player in determining the occurrence of APOs in obstetric APS, while its role in thrombotic APS despite gaining increased interest still remains unclear.

Complement activation has been shown to be associated with a higher risk of TE in APS while increased complement

Table 1. Studies investigating the association between complement and aPL/APS

Authors	Number of pts	Complement components/complement regulatory factors detected or functional assays used	Main findings
Oku *et al.* 2009 [25]	36 PAPS, 36 HC, 42 non-SLE CTD	C3, C4, CH50, C3a, C4a, C5a	• C3, C4, CH50 levels were significantly lower in PAPS pts *vs* non-SLE CTD • PAPS pts with low C3 had significantly higher levels of C3a than those with normal C3
Peerschke *et al.* 2009 [65]	91 SLE without aPL, 27 SLE with aPL without APS, 51 SLE-APS, 57 primary aPL without APS, 96 PAPS, 50 HC	Deposition of C1q and C4d on platelets	• Sera from SLE without aPL pts and aPL/APS pts led to a significantly higher C1q deposition on heterologous platelets compared with controls • Sera with high levels of classical pathway activation were able to activate platelets • C4d deposition on platelets was significantly associated with AT in SLE with aPL, but not in pts without SLE
Breen *et al.* 2012 [27]	186 aPL/PAPS, 30 HC	Fragment Bb, C3a-desArg	• Patients with aPL positivity had significantly higher levels of fragment Bb and C3a compared with HC • Fragment Bb and C3a levels were not higher in the aPL-positive patients without APS-related events compared with the APS patients • Fragment Bb and C3a levels correlated with persistently positive LA and double/triple aPL positivity
Lood *et al.* 2014 [66]	148 SLE (some of them with aPL+: at visit 5% aCL+, 7% aβ2GPI, 11% LA+), 20 RA, 20 SSc, 79 HC, 39 MI without chronic inflammatory disease	Deposition of C1q and C4d on platelets	• C4d deposition on platelets in SLE patients with aPL+ was significantly higher than in SLE patients without aPL
Kao *et al.* 2014 [89]	356 SLE	C4d bound to platelets	• PC4d was significantly associated with all-cause mortality (HR 7.52, 95% CI 2.14–26.45) • PC4d was significantly associated with ischemic stroke after adjusting for antiphospholipid status (OR 4.54, 95% CI 1.63–12.69)
Foltyn Zadura *et al.* 2015 [78]	Serbian cohort: 73 PAPS, 33 SAPS; Italian cohort: 15 PAPS, 25 SAPS; 155 HC	FH autoantibodies	• FH autoantibodies levels were significantly higher in APS pts *vs* HC • Pts with FH autoantibodies had a significantly higher risk of recurrent VTE (HR 2.0, 95% CI 1.2–3.3) compared with those without FH autoantibodies
Nakamura *et al.* 2018 [76]	27 PAPS, 20 SLE-APS, 24 SLE, 25 CTD other than SLE	C3, C4, MCP, FH	• Significantly lower FH levels in PAPS compared with pts without history of aPL-related TE • In PAPS: significant positive correlation between FH levels and C3 ($r = 0.55$)
Kim *et al.* 2018 [87]	487 pregnant SLE and/or aPL+ pts, 204 pregnant HC	Bb, C5b-9	• Significantly higher Bb and C5b-9 levels at 12-15 weeks in SLE and/or aPL pts with APOs compared with pts without APOs • After adjusting for other risk factors for APOs, Bb and C5b-9 levels at 12–15 weeks remained significantly associated with APOs
Lonati *et al.* 2019 [41]	23 PAPS, 11 SAPS, 17 aPL-positive SLE, 16 aPL-negative SLE; controls: 11 ITP, 8 aPL-negative with previous TE, 8 aPL carriers, 26 HC	C4d bound to B lymphocytes, erythrocytes, platelets	• A significant inverse correlation was found between serum C4 and PC4d ($r = -0.4682$, $P < 0.0001$) and between serum C4 and EC4d ($r = -0.5163$, $P < 0.0001$)

(continued)

Table 1. (continued)

Authors	Number of pts	Complement components/complement regulatory factors detected or functional assays used	Main findings
			• Significantly higher proportions of EC4d and PC4d were detected in aPL+ SLE, SLE-associated APS, PAPS *vs* controls • Significant correlations between PC4d and aβ2GPI IgG (r = 0.2486), aCL IgG (r = 0.4537), aCL IgM (r = 0.2472) • Significant correlations between EC4d and aβ2GPI IgG (r = 0.3503), aCL IgG (r = 0.4805), aβ2GPI IgM (r = 0.2672), aCL IgM (r = 0.4177) • Aβ2GPI IgG and EC4d aCL IgG titer significantly correlated with EC4d • Pathogenic aPLs bound active platelets more easily than resting platelets
Savelli *et al.* 2019 [77]	359 APS, 166 aPL carriers (293 had SLE)	C3, C4, FH, MBL	• Significantly higher C4, C4a, C4b, C3 in APS pts *vs* aPL carriers • Significantly lower levels of FH and MBL in APS pts *vs* aPL carriers
Chaturvedi *et al.* 2020 [39]	59 thrombotic APS, 10 CAPS, 74 SLE, 33 aHUS (positive controls), 43 individuals without complement-mediated disorder (negative controls)	C5b-9 deposition, mHam assay (terminal pathway activation)	• mHam+ in 85.7% CAPS, 35.6% APS, 6.8% SLE ($P < 0.001$) • The activation of the complement cascade was mostly due to the classical pathway • Significant association between mHam+ >1 year after TE and recurrent VTE
Svenungsson *et al.* 2020 [42]	308 SLE, 308 HC	C4d bound to platelets	• Variants in the genes of the complement alternative pathway were found in 60% CAPS, a significantly higher proportion compared with thrombotic APS (21.8%), and compared with HC (23.3%) • Significantly greater deposition of PC4d in SLE *vs* controls, 50% *vs* 5%, respectively • Significant association between PC4d+ and any vascular event, ischaemic stroke, and any VTE: OR (95% CI): 2.9 (1.7, 4.9), 2.6 (1.03, 6.4), 2.9 (1.5, 5.8), respectively • Synergic effect due to the concomitant presence of PC4d+ and LA+
Nalli *et al.* 2021 [86]	333 APS, 50 aPL carriers	C3, C4	• Patients with complicated pregnancy had significantly lower preconception C3/C4 compared with pts with uncomplicated pregnancy • Pts with low preconception C3/C4 were more likely to have pregnancy losses and preterm delivery
Gartshteyn *et al.* 2021 [90]	150 SLE	C4d bound to platelets	• Significant association between PC4d and arterial events after adjusting for antiphospholipid status (OR 1.71, 95% CI 1.91–2.89)
Ruffatti *et al.* 2021 [30]	7 CAPS, 8 HC	C5b-9, C5a	• C5b-9 and C5a are significantly higher in quiescent CAPS than in thrombotic APS and HC
Ruffatti *et al.* 2022 [88]	62 quiescent APS (40 thrombotic APS, 13 RAPS, 9 CAPS), 30 HC	C5a, C5b-9	• Significantly lower levels of C5a and C5b-9 in thrombotic APS *vs* RAPS/CAPS, in quiescent APS *vs* active APS • Significantly higher levels of C5a in pts with small vessel thrombosis *vs* VTE • Significantly higher levels of C5b-9 in pts with small vessel thrombosis *vs* VTE and AT, in triple aPL+ pts *vs* single or double aPL+ pts

(continued)

Table 1. (continued)

Authors	Number of pts	Complement components/complement regulatory factors detected or functional assays used	Main findings
Ponce *et al.* 2022 [91]	73 CAPS (of whom 29 with SLE)	C3, C4	• 58% ($n = 42$) CAPS pts has low C3/C4 during the acute phase of the disease
Naranjo *et al.* 2022 [44]	165 PAPS, 138 APS associated with other systemic autoimmune diseases (of whom 112 with SLE)	C3, C4, C3a, C5a	• C3 and C4 levels significantly higher in B2-CIC-negative pts *vs* B2-CIC-positive pts
Zen *et al.* 2023 [32]	37 OAPS, 38 primary thrombotic APS, 42 aPL carriers, 30 HC	C5a, C5b-9	• C5a and C5b-9 levels were significantly higher in OAPS, thrombotic APS, aPL carriers compared with controls • C5a median levels were significantly higher in patients with aβ2GPI IgG at high levels of *vs* medium levels • C5b-9 median levels were significantly higher in pts with >1 aPL positivity *vs* pts with single aPL positivity, pts with triple positivity *vs* pts with single/double positivity, pts with IgG aCL at high levels *vs* medium levels, pts with aβ2GPI IgG at high levels of *vs* medium levels • No significant difference in the levels of C5a and C5b-9 between arterial thrombotic APS and venous thrombotic APS
Yelnik *et al.* 2023 [45]	98 APS, 25 HC	C3a, C4a, C5b-9, Bb	• C3a, C4a, C5b-9, Bb levels were significantly higher in APS patients than in controls • Elevated Bb levels were significantly associated with triple positivity
Vils *et al.* 2023 [67]	17 PAPS, 20 SLE, 39 HC	C3, C4, LPPs (including MAPS-2, L-ficolin)	• MASP-2 levels correlated negatively with platelet activation in APS pts, but not in SLE pts
Zuo *et al.* 2023 [75]	308 PAPS, 81 pts with aPL+, 40 HC	Circulating C3 and C4, C4d deposition	• Significant negative correlation between C3/C4 and anti-NET IgM (r = –0.12 for C3; r = –0.13 for C4) • Serum samples with high anti-NET IgM showed higher deposition of C3d on NETs compared with control samples
Esteve-Valverde *et al.* 2023 [84]	1048 OAPS	C3, C4	• Significantly higher proportion of OAPS women with LC had late fetal growth restriction and fetal losses compared with NC • Significantly higher incidence of live birth in OAPS women with NC compared with LC • Significantly shorter duration of pregnancy in OAPS pts with LC compared with NC

aβ2GPI: anti-β2 glicoprotein I antibodies; aHUS: atypical haemolytic uraemic syndrome; APOs: adverse pregnancy outcomes; AT: arterial thrombosis; B2-CIC circulating immune-complexes formed by beta-2-glycoprotein-I and anti-B2GP1 antibodies; EC4d: C4d bound to erythrocytes; CAPS: catastrophic APS; FH: factor H; HC: healthy controls; HR: hazard ratio; ITP: immune thrombocytopenia; LC: low complement; LPPs: lectin pathway proteins; MASP: MBL-associated serine protein; MBL: mannose-binding lectin; MCP: membrane cofactor protein; mHam: modified Ham test; MI: myocardial infarction; NC: normal complement; NETP: neutrophil extracellular traps; OAPS: obstetric APS; OR: odds ratio; PAPS: primary APS; PC4d: C4d bound to platelets; pts: patients; SAPS: secondary APS; TE: thrombotic events; *vs*: *vs*; VTE: venous thromboembolism.

activation has also been reported in both refractory APS and CAPS patients well outside the acute thrombotic phase of the disease.

However, the extent and degree that complement activation contributes to the heterogeneous clinical APS manifestations and its applicability as a therapeutic target remain to be elucidated.

A complex interplay between aPL, complement and platelets has been implicated in thrombotic APS. Recent studies have explored the influence of different platelet subpopulations on the risk of recurrent ischemic events in non-APS patients, identifying coated (subpopulation of platelets detected after stimulation with both collagen and thrombin) and procoagulant platelets as giving an increased risk

[98, 99]. The role of platelet-derived complement activation in APS patients has not yet been investigated, but it could be crucial for a subset of patients that could benefit from complement inhibition to reduce platelet activation.

Based on recent findings we believe that complement inhibition has a great potential as therapeutic target in APS, but research is still in its infancy. Further mechanistic and clinical studies are required to delineate the exact role of complement and the efficacy of complement inhibition in the different APS clinical manifestations, as well as further studies to identify the best laboratory tests for its detection in clinical practice. This can ultimately lead to identification of markers that can improve risk stratification in APS patients at risk of recurrent thrombosis or CAPS. Complement inhibition should be adjunctive to current therapy to improve outcomes in certain patients and can ultimately lead to patient-tailored targeted therapy depending on which pathway is involved in the different clinical APS manifestations.

Data availability

No new data were generated or analysed in support of this article.

Funding

No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement: The authors have declared no relevant conflicts of interest.

References

1. Cervera R, Serrano R, Pons-Estel GJ; Euro-Phospholipid Project Group (European Forum on Antiphospholipid Antibodies) *et al.* Morbidity and mortality in the antiphospholipid syndrome during a 10-year period: a multicentre prospective study of 1000 patients. Ann Rheum Dis 2015;74:1011–8.
2. Cervera R, Khamashta MA, Font J, European Working Party on Systemic Lupus Erythematosus *et al.* Morbidity and Mortality in Systemic Lupus Erythematosus During a 10-Year Period: a Comparison of Early and Late Manifestations in a Cohort of 1,000 Patients. Medicine 2003;82:299–308.
3. Barbhaiya M, Zuily S, Naden R, ACR/EULAR APS Classification Criteria Collaborators *et al.* 2023 ACR/EULAR antiphospholipid syndrome classification criteria. Ann Rheum Dis 2023; 82:1258–70.
4. Pons-Estel GJ, Andreoli L, Scanzi F, Cervera R, Tincani A. The antiphospholipid syndrome in patients with systemic lupus erythematosus. J Autoimm 2017;76:10–20.
5. Pengo V, Biasiolo A, Pegoraro C *et al.* Antibody profiles for the diagnosis of antiphospholipid syndrome. Thromb Haemost 2005; 93:1147–52.
6. Tektonidou MG, Andreoli L, Limper M *et al.* EULAR recommendations for the management of antiphospholipid syndrome in adults. Ann Rheum Dis 2019;78:1296–304.
7. Taraborelli M, Reggia R, Dall'Ara F *et al.* Longterm outcome of patients with primary antiphospholipid syndrome: a retrospective multicenter study. J Rheumatol 2017;44:1165–72.
8. Turiel M, Sarzi-Puttini P, Peretti R *et al.* Thrombotic risk factors in primary antiphospholipid syndrome: a 5-year prospective study. Stroke 2005;36:1490–4.
9. Ortel TL, Meleth S, Catellier D *et al.* Recurrent thrombosis in patients with antiphospholipid antibodies and an initial venous or arterial thromboembolic event: a systematic review and meta-analysis. J Thromb Haemost 2020;18:2274–86.
10. Efthymiou M, Arachchillage DRJ, Lane PJ *et al.* Antibodies against TFPI and protein C are associated with a severe thrombotic phenotype in patients with and without antiphospholipid syndrome. Thrombosis Research 2018;170:60–8. https://doi.org/10.1016/j.thromres.2018.08.003.
11. Arachchillage DRJ, Efthymiou M, Mackie IJ *et al.* Anti-protein C antibodies are associated with resistance to endogenous protein C activation and a severe thrombotic phenotype in antiphospholipid syndrome. Journal of Thrombosis and Haemostasis 2014; 12:1801–9.
12. Amengual O, Atsumi T, Khamashta M, Hughes G. The role of the tissue factor pathway in the hypercoagulable state in patients with the antiphospholipid syndrome. Thromb Haemost 1998; 79:276–81.
13. Kinev A, Roubey R. Tissue factor in the antiphospholipid syndrome. Lupus 2008;17:952–8.
14. Baroni G, Banzato A, Bison E *et al.* The role of platelets in antiphospholipid syndrome. Platelets 2017;28:762–6.
15. Han Z, Liu Q, Li H *et al.* The role of monocytes in thrombotic diseases: a review. Front Cardiovasc Med 2023;10:1113827.
16. Velásquez M, Peláez LF, Rojas M *et al.* Differences in endothelial activation and dysfunction induced by antiphospholipid antibodies among groups of patients with thrombotic, refractory, and non-refractory antiphospholipid syndrome. Front Physiol 2021; 12:764702.
17. Meng H, Yalavarthi S, Kanthi Y *et al.* In vivo role of neutrophil extracellular traps in antiphospholipid antibody–mediated venous thrombosis. Arthr Rheumatol 2017;69:655–67.
18. Ahmed K, Vianna J, Khamashta M, Hughes G. IL-2, IL-6 and TNF levels in primary antiphospholipid syndrome. Clin Exp Rheumatol 1992;10:503.
19. Tedesco F, Borghi MO, Gerosa M *et al.* Pathogenic role of complement in antiphospholipid syndrome and therapeutic implications. Front Immunol 2018;9:1388.
20. Manderson AP, Botto M, Walport MJ. The role of complement in the development of systemic lupus erythematosus. Annu Rev Immunol 2004;22:431–56.
21. Pryzdial ELG, Leatherdale A, Conway EM. Coagulation and complement: key innate defense participants in a seamless web. Front Immunol 2022;13:918775.
22. Chaturvedi S, Brodsky RA, McCrae KR. Complement in the pathophysiology of the antiphospholipid syndrome. Front Immunol 2019;10:449.
23. Mastellos DC, Hajishengallis G, Lambris JD. A guide to complement biology, pathology and therapeutic opportunity. Nat Rev Immunol 2023;24:118–41.
24. Chaturvedi S, Braunstein EM, Brodsky RA. Antiphospholipid syndrome: complement activation, complement gene mutations, and therapeutic implications. Journal of Thrombosis and Haemostasis 2021;19:607–16.
25. Oku K, Atsumi T, Bohgaki M *et al.* Complement activation in patients with primary antiphospholipid syndrome. Annals of the Rheumatic Diseases 2009;68:1030–5.
26. Munakata Y, Saito T, Matsuda K *et al.* Detection of complement-fixing antiphospholipid antibodies in association with thrombosis. Thromb Haemost 2000;83:728–31.
27. Breen KA, Seed P, Parmar K *et al.* Complement activation in patients with isolated antiphospholipid antibodies or primary antiphospholipid syndrome. Thromb Haemost 2012;107:423–9.
28. Davis W, Brey R. Antiphospholipid antibodies and complement activation in patients with cerebral ischemia. Clin Exp Rheumatol 1992;10:455–60.
29. Barratt-Due A, Fløisand Y, Orrem HL *et al.* Complement activation is a crucial pathogenic factor in catastrophic antiphospholipid syndrome. Rheumatology 2016;55:1337–9.
30. Ruffatti A, Tonello M, Macor P *et al.* Markers of complement activation in plasma during quiescent phases in patients with

catastrophic antiphospholipid syndrome. Blood 2021;137:2989–92. https://doi.org/10.1182/blood.2020010575.
31. Pengo V, Ruffatti A, Legnani C *et al.* Incidence of a first thromboembolic event in asymptomatic carriers of high-risk antiphospholipid antibody profile: a multicenter prospective study. Blood 2011;118:4714–8.
32. Zen M, Tonello M, Favaro M *et al.* Antiphospholipid antibody carriers and patients with quiescent antiphospholipid syndrome show persistent subclinical complement activation. Rheumatology 2023;kead517.
33. Grosso G, Sandholm K, Antovic A *et al.* The complex relationship between C4b-binding protein, warfarin, and antiphospholipid antibodies. Thromb Haemost 2021;121:1299–309.
34. Girardi G, Redecha P, Salmon JE. Heparin prevents antiphospholipid antibody–induced fetal loss by inhibiting complement activation. Nat Med 2004;10:1222–6.
35. Weiler JM, Edens RE, Linhardt RJ, Kapelanski DP. Heparin and modified heparin inhibit complement activation in vivo. J Immunol 1992;148:3210–5.
36. Gavriilaki E, Brodsky RA. Complementopathies and precision medicine. Journal of Clinical Investigation 2020;130:2152–63.
37. Gavriilaki E, Yuan X, Ye Z *et al.* Modified Ham test for atypical hemolytic uremic syndrome. Blood 2015;125:3637–46.
38. Yuan X, Yu J, Gerber G *et al.* Ex vivo assays to detect complement activation in complementopathies. Clinical Immunology 2020;221:108616. https://doi.org/10.1016/j.clim.2020.108616.
39. Chaturvedi S, Braunstein EM, Yuan X *et al.* Complement activity and complement regulatory gene mutations are associated with thrombosis in APS and CAPS. Blood 2020;135:239–51. https://doi.org/10.1182/blood.2019003863.
40. Murata K, Baldwin WM. Mechanisms of complement activation, C4d deposition, and their contribution to the pathogenesis of antibody-mediated rejection. Transplant Rev 2009;23:139–50. https://doi.org/10.1016/j.trre.2009.02.005.
41. Lonati PA, Scavone M, Gerosa M *et al.* Blood cell-bound C4d as a marker of complement activation in patients with the antiphospholipid syndrome. Front Immunol 2019;10:773.
42. Svenungsson E, Gustafsson JT, Grosso G *et al.* Complement deposition, C4d, on platelets is associated with vascular events in systemic lupus erythematosus. Rheumatology 2020;59:3264–74.
43. Agostinis C, Durigutto P, Sblattero D *et al.* A non–complement-fixing antibody to β2 glycoprotein I as a novel therapy for antiphospholipid syndrome. Blood 2014;123:3478–87.
44. Naranjo L, Stojanovich L, Djokovic A *et al.* Circulating immune-complexes of IgG/IgM bound to B2-glycoprotein-I associated with complement consumption and thrombocytopenia in antiphospholipid syndrome. Front Immunol 2022;13:957201.
45. Yelnik CM, Lambert M, Drumez E *et al.* Relevance of inflammatory and complement activation biomarkers profiling in antiphospholipid syndrome patients outside acute thrombosis. Clinical and Experimental Rheumatology 2023;41:1875–81.
46. Conway EM. Complement-coagulation connections. Blood Coagul Fibrinolysis 2018;29:243–51.
47. Gale AJ. Current understanding of hemostasis. Toxicol Pathol 2011;39:273–80.
48. Ruggeri ZM, Mendolicchio GL. Adhesion mechanisms in platelet function. Circ Res 2007;100:1673–85.
49. Bourguignon A, Tasneem S, Hayward CPM. Update on platelet procoagulant mechanisms in health and in bleeding disorders. Int J Lab Hematology 2022;44:89–100.
50. Hamad OA, Ekdahl KN, Nilsson PH *et al.* Complement activation triggered by chondroitin sulfate released by thrombin receptor-activated platelets. J Thromb Haemost 2008;6:1413–21.
51. Blair P, Flaumenhaft R. Platelet α-granules: basic biology and clinical correlates. Blood Reviews 2009;23:177–89.
52. Eriksson O, Mohlin C, Nilsson B, Ekdahl KN. The Human Platelet as an Innate Immune Cell: interactions Between Activated Platelets and the Complement System. Front Immunol 2019;10:1590.
53. Heurich M, McCluskey G. Complement and coagulation cross-talk—Factor H in the spotlight. Immunobiology 2023;228:152707.
54. Kozarcanin H, Lood C, Munthe-Fog L *et al.* The lectin complement pathway serine proteases (MASPs) represent a possible crossroad between the coagulation and complement systems in thromboinflammation. J Thromb Haemost 2016;14:531–45.
55. Riedl M, Noone DG, Khan MA *et al.* Complement activation induces neutrophil adhesion and neutrophil-platelet aggregate formation on vascular endothelial cells. Kidney Int Rep 2017;2:66–75.
56. Oikonomopoulou K, Ricklin D, Ward PA, Lambris JD. Interactions between coagulation and complement—their role in inflammation. Semin Immunopathol 2012;34:151–65. https://doi.org/10.1007/s00281-011-0280-x.
57. Schreiber K, Sciascia S, de Groot PG *et al.* Antiphospholipid syndrome. Nat Rev Dis Primers 2018;4:17103.
58. López-Pedrera C, Buendía P, José Cuadrado M *et al.* Antiphospholipid antibodies from patients with the antiphospholipid syndrome induce monocyte tissue factor expression through the simultaneous activation of NF-κB/Rel proteins via the p38 mitogen-activated protein kinase pathway, and of the MEK-1/ERK pathway. Arthr Rheum 2006;54:301–11.
59. Müller-Calleja N, Hollerbach A, Ritter S *et al.* Tissue factor pathway inhibitor primes monocytes for antiphospholipid antibody-induced thrombosis. Blood 2019;134:1119–31.
60. Ritis K, Doumas M, Mastellos D *et al.* A Novel C5a Receptor-Tissue Factor Cross-Talk in Neutrophils Links Innate Immunity to Coagulation Pathways. The Journal of Immunology 2006;177:4794–802.
61. Saadi S, Holzknecht RA, Patte CP, Stern DM, Platt JL. Complement-mediated regulation of tissue factor activity in endothelium. J Exp Med 1995;182:1807–14.
62. Ruf W. Links between complement activation and thrombosis. Blood 2019;134:SCI-40—40.
63. Wiedmer T, Esmon CT, Sims PJ. Complement proteins C5b-9 stimulate procoagulant activity through platelet prothrombinase. Blood 1986;68:875–80.
64. Wiedmer T, Ando B, Sims PJ. On the mechanism by which complement proteins C5b-9 increase platelet prothrombinase activity. J Biol Chem 1986;262:13674–81.
65. Peerschke E, Yin W, Alpert D *et al.* Serum complement activation on heterologous platelets is associated with arterial thrombosis in patients with systemic lupus erythematosus and antiphospholipid antibodies. Lupus 2009;18:530–8. https://doi.org/10.1177/0961203308099974.
66. Lood C, Tydén H, Gullstrand B *et al.* Platelet activation and antiphospholipid antibodies collaborate in the activation of the complement system on platelets in systemic lupus erythematosus. PLoS ONE 2014;9:e99386.
67. Vils SR, Troldborg A, Hvas A-M, Thiel S. Platelets and the lectin pathway of complement activation in patients with systemic lupus erythematosus or antiphospholipid syndrome. TH Open 2023;7:e155–67–e167.
68. Mannes M, Pechtl V, Hafner S *et al.* Complement & platelets: prothrombotic cell activation requires membrane attack complex induced release of danger signals. Blood Adv 2023;7:6367–80.
69. Peerschke EIB, Yin W, Grigg SE, Ghebrehiwet B. Blood platelets activate the classical pathway of human complement. J Thromb Haemost 2006;4:2035–42.
70. Amara U, Flierl MA, Rittirsch D *et al.* Molecular intercommunication between the complement and coagulation systems. J Immunol 2010;185:5628–36.
71. Papayannopoulos V. Neutrophil extracellular traps in immunity and disease. Nat Rev Immunol 2018;18:134–47.
72. Tambralli A, Gockman K, Knight JS. NETs in APS: current knowledge and future perspectives. Curr Rheumatol Rep 2020;22:67.
73. Yalavarthi S, Gould TJ, Rao AN *et al.* Release of neutrophil extracellular traps by neutrophils stimulated with antiphospholipid

antibodies: a newly identified mechanism of thrombosis in the antiphospholipid syndrome. Arthr Rheumatol 2015; 67:2990–3003.
74. Zuo Y, Yalavarthi S, Gockman K *et al.* Anti–neutrophil extracellular trap antibodies and impaired neutrophil extracellular trap degradation in antiphospholipid syndrome. Arthr Rheumatol 2020; 72:2130–5.
75. Zuo Y, Navaz S, Tsodikov A; Antiphospholipid Syndrome Alliance for Clinical Trials and InternatiOnal Networking *et al.* Anti–neutrophil extracellular trap antibodies in antiphospholipid antibody–positive patients: results from the antiphospholipid syndrome alliance for clinical trials and International Networking Clinical Database and Repository. Arthr Rheumatol 2023; 75:1407–14.
76. Nakamura H, Oku K, Ogata Y *et al.* Alternative pathway activation due to low level of complement factor H in primary antiphospholipid syndrome. Thromb Res 2018;164:63–8.
77. Savelli SL, Roubey RAS, Kitzmiller KJ *et al.* Opposite profiles of complement in antiphospholipid syndrome (APS) and systemic lupus erythematosus (SLE) among patients with antiphospholipid antibodies (aPL). Front Immunol 2019;10:885.
78. Foltyn Zadura A, Memon AA, Stojanovich L *et al.* Factor H autoantibodies in patients with antiphospholipid syndrome and thrombosis. J Rheumatol 2015;42:1786–93.
79. Holers VM, Girardi G, Mo L *et al.* Complement C3 activation is required for antiphospholipid antibody-induced fetal loss. J Exp Med 2002;195:211–20.
80. Girardi G, Berman J, Redecha P *et al.* Complement C5a receptors and neutrophils mediate fetal injury in the antiphospholipid syndrome. J Clin Invest 2003;112:1644–54.
81. Viall CA, Chamley LW. Histopathology in the placentae of women with antiphospholipid antibodies: a systematic review of the literature. Autoimm Rev 2015;14:446–71.
82. Lublin DM, Atkinson JP. Decay-accelerating factor: biochemistry, molecular biology, and function. Annu Rev Immunol 1989; 7:35–58.
83. Alijotas-Reig J, Ferrer-Oliveras R; EUROAPS Study Group. The European Registry on Obstetric Antiphospholipid Syndrome (EUROAPS): a preliminary first year report. Lupus 2012; 21:766–8.
84. Esteve-Valverde E, Alijotas-Reig J, Belizna C *et al.* Low complement levels are related to poor obstetric outcomes in women with obstetric antiphospholipid syndrome. The EUROAPS Registry Study Group. Placenta 2023;136:29–34.
85. Deguchi M, Yamada H, Sugiura-Ogasawara M *et al.* Factors associated with adverse pregnancy outcomes in women with antiphospholipid syndrome: a multicenter study. J Reprod Immunol 2017; 122:21–7.
86. Nalli C, Lini D, Andreoli L *et al.* Low preconception complement levels are associated with adverse pregnancy outcomes in a multicenter study of 260 pregnancies in 197 women with antiphospholipid syndrome or carriers of antiphospholipid antibodies. Biomedicines 2021;9:671.
87. Kim MY, Guerra MM, Kaplowitz E *et al.* Complement activation predicts adverse pregnancy outcome in patients with systemic lupus erythematosus and/or antiphospholipid antibodies. Ann Rheum Dis 2018;77:549–55.
88. Ruffatti A, Tonello M, Calligaro A *et al.* High plasma C5a and C5b-9 levels during quiescent phases are associated to severe antiphospholipid syndrome subsets. Clinic Exp Rheumatol 2022; 40:2088–96.
89. Kao AH, McBurney CA, Sattar A *et al.* Relation of platelet C4d with all-cause mortality and ischemic stroke in patients with systemic lupus erythematosus. Transl Stroke Res 2014;5:510–8.
90. Gartshteyn Y, Mor A, Shimbo D *et al.* Platelet bound complement split product (PC4d) is a marker of platelet activation and arterial vascular events in systemic lupus erythematosus. Clin Immunol 2021;228:108755.
91. Ponce A, Rodríguez-Pintó I, Basauli JM; On Behalf the CAPS Registry Project Group/European Forum on Antiphospholipid Antibodies *et al.* The clinical significance of low complement levels in patients with catastrophic antiphospholipid syndrome: A descriptive analysis of 73 patients from the "Catastrophic antiphospholipid syndrome registry". Lupus 2022;31:1218–25.
92. Legault K, Schunemann H, Hillis C *et al.* McMaster RARE-Bestpractices clinical practice guideline on diagnosis and management of the catastrophic antiphospholipid syndrome. J Thromb Haemost 2018;16:1656–64.
93. López-Benjume B, Rodríguez-Pintó I, Amigo MC; on behalf the CAPS Registry Project Group/European Forum on Antiphospholipid Antibodies *et al.* Eculizumab use in catastrophic antiphospholipid syndrome (CAPS): descriptive analysis from the "CAPS Registry". Autoimm Rev 2022;21:103055.
94. Ter Avest M, Bouwmeester RN, Duineveld C; CUREiHUS study group *et al.* Proposal for individualized dosing of eculizumab in atypical haemolytic uraemic syndrome: patient friendly and cost-effective. Nephrol Dial Transplant 2023;38:362–71.
95. Hussain H, Tarantino MD, Chaturvedi S, McCrae KR, Roberts JC. Eculizumab for refractory thrombosis in antiphospholipid syndrome. Blood Adv 2022;6:1271–7.
96. Kelly RJ, Höchsmann B, Szer J *et al.* Eculizumab in pregnant patients with paroxysmal nocturnal hemoglobinuria. N Engl J Med 2015;373:1032–9.
97. Gustavsen A, Skattum L, Bergseth G *et al.* Effect on mother and child of eculizumab given before caesarean section in a patient with severe antiphospholipid syndrome: a case report. Medicine 2017;96:e6338.
98. Prodan CI, Stoner JA, Cowan LD, Dale GL. Higher coated-platelet levels are associated with stroke recurrence following nonlacunar brain infarction. J Cereb Blood Flow Metab 2013;33:287–92.
99. Kirkpatrick AC, Vincent AS, Dale GL, Prodan CI. Coated-platelets predict stroke at 30 days following TIA. Neurology 2017;89:125–8.

Rheumatology, 2024, 00, 1–12
https://doi.org/10.1093/rheumatology/keae178
Review

Consistent safety profile with over 8 years of real-world evidence, across licensed indications[1–3]

Cosentyx® secukinumab

1,000,000 patients treated globally, and counting*[4]

100+ clinical trials*[5]

8+ years of real-world evidence[1–3]

8 indications[1–3]

Click here to visit our HCP portal and learn more

Real-world evidence shows a consistent safety profile over 6 years[6,7]

No trend toward increased AE rates over time (pooled PsA, AS, PsO):†[6]

AEs of select interest (EAIR per 100 PY)	1 year	2 years	3 years	4 years	5 years	6 years	Cumulative rate
Serious infections Cases	2.0 n=149	1.7 n=475	0.7 n=649	1.3 n=1,841	1.3 n=2,285	1.1 n=2,226	1.3 n=8,719
Malignant or unspecified tumours Cases	0.2 n=15	0.2 n=50	0.2 n=225	0.3 n=422	0.3 n=520	0.3 n=573	0.3 n=1,896
MACE Cases	0.2 n=15	0.1 n=39	0.2 n=151	0.2 n=238	0.2 n=264	0.1 n=287	0.2 n=1,031
Total IBD Cases	0.2 n=12	0.2 n=46	0.2 n=185	0.3 n=340	0.2 n=312	0.1 n=261	0.2 n=1,291
Exposure (PY)	7450	28,549	93,744	137,325	182,024	212,636	680,470

No trend towards increased rates of malignancy, MACE or IBD over time[6]

The most frequently reported adverse reactions are upper respiratory tract infections (17.1%) (most frequently nasopharyngitis, rhinitis).[1,2] Refer to the prescribing information for a summary of adverse events.

Adapted from Novartis Data on File. 2021.[6]

Refer to the Cosentyx Summary of Product Characteristics for full details, dosing and administration, including special populations.

Cosentyx® (secukinumab) licensed indications in rheumatology: Cosentyx, alone or in combination with methotrexate, is indicated for the treatment of active **psoriatic arthritis** in adult patients when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate; active **ankylosing spondylitis** in adults who have responded inadequately to conventional therapy; active **non-radiographic axial spondyloarthritis** with objective signs of inflammation as indicated by elevated C-reactive protein and/or magnetic resonance imaging evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs; active **enthesitis-related arthritis** in patients 6 years and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate conventional therapy; active **juvenile psoriatic arthritis** in patients 6 years or older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy.[1,2]

Prescribing information, adverse event reporting and full indication can be found on the next page.

*Patients prescribed Cosentyx for any indication since launch.

†Successive time periods of PSUR shown with cumulative rate: 26 Dec 2014 to 25 Dec 2015; 26 Dec 2015 to 25 Dec 2016; 26 Dec 2016 to 25 Dec 2017; 26 Dec 2017 to 25 Dec 2018: 26 Dec 2018 to 25 Dec 2019; 26 Dec 2019 to 25 Dec 2020.[6]

Abbreviations: AE, adverse event; AS, ankylosing spondylitis; EIAR, exposure-adjusted incidence rate; HCP, healthcare professional; IBD, inflammatory bowel disease; MACE, major adverse cardiac event; PsA, psoriatic arthritis; PsO, plaque psoriasis; PY, patient year.

References: 1. Cosentyx® (secukinumab) GB Summary of Product Characteristics; **2.** Cosentyx® (secukinumab) NI Summary of Product Characteristics; **3.** European Medicines Agency. European public assessment report. Available at: https://www.ema.europa.eu/en/documents/overview/cosentyx-epar-medicine-overview_en.pdf [Accessed February 2024]; **4.** Novartis Data on File. Secukinumab – Sec008. 2023; **5.** Novartis. Novartis Cosentyx® positive 16-week PREVENT results advance potential new indication for patients with axial spondyloarthritis. Available at: https://www.novartis.com/news/media-releases/novartis-cosentyx-positive-16-week-prevent-results-advance-potential-new-indication-patients-axial-spondyloarthritis [Accessed February 2024]; **6.** Novartis data on file. Cosentyx Periodic Safety Update Report (PSUR); 26 December 2019 – 25 December 2020. 22 February 2021; **7.** Deodhar A, et al. Arthritis Res Ther 2019;21(1):111.

NOVARTIS

UK | February 2024 | 407722

Cosentyx® (secukinumab) Northern Ireland Prescribing Information.

Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Indications: Treatment of: moderate to severe plaque psoriasis in adults, children and adolescents from the age of 6 years who are candidates for systemic therapy; active psoriatic arthritis in adults (alone or in combination with methotrexate) who have responded inadequately to disease-modifying anti-rheumatic drug therapy; active ankylosing spondylitis in adults who have responded inadequately to conventional therapy; active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs; active enthesitis-related arthritis and juvenile psoriatic arthritis in patients 6 years and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy; active moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic HS therapy. **Presentations:** Cosentyx 150 mg solution for injection in pre-filled pen; Cosentyx 300 mg solution for injection in pre-filled pen. **Dosage & Administration:** Administered by subcutaneous injection at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Consider discontinuation if no response after 16 weeks of treatment. Each 150 mg dose is given as one injection of 150 mg. Each 300 mg dose is given as two injections of 150 mg or one injection of 300 mg. If possible avoid areas of the skin showing psoriasis. *Plaque Psoriasis:* Adult recommended dose is 300 mg monthly. Based on clinical response, a maintenance dose of 300 mg every 2 weeks may provide additional benefit for patients with a body weight of 90 kg or higher. Adolescents and children from the age of 6 years: if weight ≥ 50 kg, recommended dose is 150 mg (may be increased to 300 mg as some patients may derive additional benefit from the higher dose). If weight < 50 kg, recommended dose is 75 mg. However, 150mg solution for injection in pre-filled pen is not indicated for administration of this dose and no suitable alternative formulation is available. *Psoriatic Arthritis:* For patients with concomitant moderate to severe plaque psoriasis see adult plaque psoriasis recommendation. For patients who are anti-TNFα inadequate responders, the recommended dose is 300 mg, 150 mg in other patients. Can be increased to 300 mg based on clinical response. *Ankylosing Spondylitis:* Recommended dose 150 mg. Can be increased to 300 mg based on clinical response. *nr-axSpA:* Recommended dose 150 mg. *Enthesitis-related arthritis and juvenile psoriatic arthritis:* From the age of 6 years, if weight ≥ 50 kg, recommended dose is 150 mg. If weight < 50 kg, recommended dose is 75 mg. However, 150mg solution for injection in pre-filled pen is not indicated for administration of this dose and no suitable alternative formulation is available. *Hidradenitis suppurativa:* Recommended dose is 300 mg monthly. Based on clinical response, the maintenance dose can be increased to 300 mg every 2 weeks. **Contraindications:** Hypersensitivity to the active substance or excipients. Clinically important, active infection. **Warnings & Precautions:** *Infections:* Potential to increase risk of infections; serious infections have been observed. Caution in patients with chronic infection or history of recurrent infection. Advise patients to seek medical advice if signs/symptoms of infection occur. Monitor patients with serious infection closely and do not administer Cosentyx until the infection resolves. Non-serious mucocutaneous candida infections were more frequently reported for secukinumab than placebo in the psoriasis clinical studies. Should not be given to patients with active tuberculosis (TB). Consider anti-tuberculosis therapy before starting Cosentyx in patients with latent TB. *Inflammatory bowel disease (including Crohn's disease and ulcerative colitis):* New cases or exacerbations of inflammatory bowel disease have been reported with secukinumab. Secukinumab, is not recommended in patients with inflammatory bowel disease. If a patient develops signs and symptoms of inflammatory bowel disease or experiences an exacerbation of pre-existing inflammatory bowel disease, secukinumab should be discontinued and appropriate medical management should be initiated. *Hypersensitivity reactions:* Rare cases of anaphylactic reactions have been observed. If an anaphylactic or serious allergic reactions occur, discontinue immediately and initiate appropriate therapy. *Vaccinations:* Do not give live vaccines concurrently with Cosentyx; inactivated or non-live vaccinations may be given. Paediatric patients should receive all age appropriate immunisations before treatment with Cosentyx. *Latex-Sensitive Individuals:* The removable needle cap of the 150mg pre-filled pen contains a derivative of natural rubber latex. *Concomitant immunosuppressive therapy:* Combination with immunosuppressants, including biologics, or phototherapy has not been evaluated in psoriasis studies. Cosentyx was given concomitantly with methotrexate, sulfasalazine and/or corticosteroids in arthritis studies. Caution when considering concomitant use of other immunosuppressants. **Interactions:** Live vaccines should not be given concurrently with secukinumab. No interaction between Cosentyx and midazolam (CYP3A4 substrate) seen in adult psoriasis study. No interaction between Cosentyx and methotrexate and/or corticosteroids seen in arthritis studies. **Fertility, pregnancy and lactation:** *Women of childbearing potential:* Use an effective method of contraception during and for at least 20 weeks after treatment. *Pregnancy:* Preferably avoid use of Cosentyx in pregnancy. *Breast feeding:* It is not known if secukinumab is excreted in human breast milk. A clinical decision should be made on continuation of breast feeding during Cosentyx treatment (and up to 20 weeks after discontinuation) based on benefit of breast feeding to the child and benefit of Cosentyx therapy to the woman. *Fertility:* Effect on human fertility not evaluated. **Adverse Reactions**: *Very Common* (≥1/10): Upper respiratory tract infection. *Common* (≥1/100 to <1/10): Oral herpes, headache, rhinorrhoea, diarrhoea, nausea, fatigue. *Uncommon (≥1/1,000 to <1/100):* Oral candidiasis, lower respiratory tract infections, neutropenia, inflammatory bowel disease. *Rare (≥1/10,000 to <1/1,000)*: anaphylactic reactions, exfoliative dermatitis (psoriasis patients), hypersensitivity vasculitis. *Not known:* Mucosal and cutaneous candidiasis (including oesophageal candidiasis). *Infections:* Most infections were non-serious and mild to moderate upper respiratory tract infections, e.g. nasopharyngitis, and did not necessitate treatment discontinuation. There was an increase in mucosal and cutaneous (including oesophageal) candidiasis, but cases were mild or moderate in severity, non-serious, responsive to standard treatment and did not necessitate treatment discontinuation. Serious infections occurred in a small proportion of patients (0.015 serious infections reported per patient year of follow up). *Neutropenia:* Neutropenia was more frequent with secukinumab than placebo, but most cases were mild, transient and reversible. Rare cases of neutropenia CTCAE Grade 4 were reported. *Hypersensitivity reactions*: Urticaria and rare cases of anaphylactic reactions were seen. *Immunogenicity:* Less than 1% of patients treated with Cosentyx developed antibodies to secukinumab up to 52 weeks of treatment. *Other Adverse Effects:* The list of adverse events is not exhaustive, please consult the SmPC for a detailed listing of all adverse events before prescribing. **Legal Category:** POM. **MA Number & List Price:** EU/1/14/980/005 - 150 mg pre-filled pen x2 £1,218.78; EU/1/14/980/010 – 300 mg pre-filled pen x 1 £1218.78. **PI Last Revised:** May 2023. Full prescribing information, (SmPC) is available from: Novartis Pharmaceuticals UK Limited, 2nd Floor, The WestWorks Building, White City Place, 195 Wood Lane, London, W12 7FQ. Telephone: (01276) 692255.

UK | 284832 | May 2023

Adverse Event Reporting:

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Novartis via uk.patientsafety@novartis.com or online through the pharmacovigilance intake (PVI) tool at www.novartis.com/report

If you have a question about the product, please contact Medical Information on 01276 698370 or by email at medinfo.uk@novartis.com

Cosentyx® (secukinumab) Great Britain Prescribing Information.

Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Indications: Treatment of: moderate to severe plaque psoriasis in adults, children and adolescents from the age of 6 years who are candidates for systemic therapy; active psoriatic arthritis in adults (alone or in combination with methotrexate) who have responded inadequately to disease-modifying anti-rheumatic drug therapy; active ankylosing spondylitis in adults who have responded inadequately to conventional therapy; active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs; active enthesitis-related arthritis and juvenile psoriatic arthritis in patients 6 years and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy; active moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic HS therapy. **Presentations:** Cosentyx 75 mg solution for injection in pre-filled syringe; Cosentyx 150 mg solution for injection in pre-filled syringe; Cosentyx 150 mg solution for injection in pre-filled pen; Cosentyx 300 mg solution for injection in pre-filled pen. **Dosage & Administration:** Administered by subcutaneous injection at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Consider discontinuation if no response after 16 weeks of treatment. Each 75 mg dose is given as one injection of 75 mg. Each 150 mg dose is given as one injection of 150 mg. Each 300 mg dose is given as two injections of 150 mg or one injection of 300 mg. If possible avoid areas of the skin showing psoriasis. *Plaque Psoriasis:* Adult recommended dose is 300 mg. Based on clinical response, a maintenance dose of 300 mg every 2 weeks may provide additional benefit for patients with a body weight of 90 kg or higher. Adolescents and children from the age of 6 years: if weight ≥ 50 kg, recommended dose is 150 mg (may be increased to 300 mg as some patients may derive additional benefit from the higher dose). If weight < 50 kg, recommended dose is 75 mg. *Psoriatic Arthritis:* For patients with concomitant moderate to severe plaque psoriasis see adult plaque psoriasis recommendation. For patients who are anti-TNFα inadequate responders, the recommended dose is 300 mg, 150 mg in other patients. Can be increased to 300 mg based on clinical response. *Ankylosing Spondylitis:* Recommended dose 150 mg. Can be increased to 300 mg based on clinical response. *nr-axSpA:* Recommended dose 150 mg. *Enthesitis-related arthritis and juvenile psoriatic arthritis:* From the age of 6 years, if weight ≥ 50 kg, recommended dose is 150 mg. If weight < 50 kg, recommended dose is 75 mg. *Hidradenitis suppurativa:* Recommended dose is 300 mg monthly. Based on clinical response, the maintenance dose can be increased to 300 mg every 2 weeks. **Contraindications:** Hypersensitivity to the active substance or excipients. Clinically important, active infection. **Warnings & Precautions:** *Infections:* Potential to increase risk of infections; serious infections have been observed. Caution in patients with chronic infection or history of recurrent infection. Advise patients to seek medical advice if signs/symptoms of infection occur. Monitor patients with serious infection closely and do not administer Cosentyx until the infection resolves. Non-serious mucocutaneous candida infections were more frequently reported for secukinumab in the psoriasis clinical studies. Should not be given to patients with active tuberculosis (TB). Consider anti-tuberculosis therapy before starting Cosentyx in patients with latent TB. *Inflammatory bowel disease (including Crohn's disease and ulcerative colitis):* New cases or exacerbations of inflammatory bowel disease have been reported with secukinumab. Secukinumab, is not recommended in patients with inflammatory bowel disease. If a patient develops signs and symptoms of inflammatory bowel disease or experiences an exacerbation of pre-existing inflammatory bowel disease, secukinumab should be discontinued and appropriate medical management should be initiated. *Hypersensitivity reactions*: Rare cases of anaphylactic reactions have been observed. If an anaphylactic or serious allergic reactions occur, discontinue immediately and initiate appropriate therapy. *Vaccinations:* Do not give live vaccines concurrently with Cosentyx; inactivated or non-live vaccinations may be given. Paediatric patients should receive all age appropriate immunisations before treatment with Cosentyx. *Latex-Sensitive Individuals*: The removable needle cap of the 75mg and 150 mg pre-filled syringe and 150mg pre-filled pen contains a derivative of natural rubber latex. *Concomitant immunosuppressive therapy:* Combination with immunosuppressants, including biologics, or phototherapy has not been evaluated in psoriasis studies. Cosentyx was given concomitantly with methotrexate, sulfasalazine and/or corticosteroids in arthritis studies. Caution when considering concomitant use of other immunosuppressants. **Interactions:** Live vaccines should not be given concurrently with secukinumab. No interaction between Cosentyx and midazolam (CYP3A4 substrate) seen in adult psoriasis study. No interaction between Cosentyx and methotrexate and/or corticosteroids seen in arthritis studies. **Fertility, pregnancy and lactation:** *Women of childbearing potential:* Use an effective method of contraception during and for at least 20 weeks after treatment. *Pregnancy:* Preferably avoid use of Cosentyx in pregnancy. *Breast feeding:* It is not known if secukinumab is excreted in human breast milk. A clinical decision should be made on continuation of breast feeding during Cosentyx treatment (and up to 20 weeks after discontinuation) based on benefit of breast feeding to the child and benefit of Cosentyx therapy to the woman. *Fertility:* Effect on human fertility not evaluated. **Adverse Reactions**: *Very Common (≥1/10):* Upper respiratory tract infection. *Common (≥1/100 to <1/10):* Oral herpes, headache, rhinorrhoea, diarrhoea, nausea, fatigue. *Uncommon (≥1/1,000 to <1/100):* Oral candidiasis, lower respiratory tract infections, neutropenia, inflammatory bowel disease. *Rare (≥1/10,000 to <1/1,000)*: anaphylactic reactions, exfoliative dermatitis (psoriasis patients), hypersensitivity vasculitis. *Not known:* Mucosal and cutaneous candidiasis (including oesophageal candidiasis). *Infections:* Most infections were non-serious and mild to moderate upper respiratory tract infections, e.g. nasopharyngitis, and did not necessitate treatment discontinuation. There was an increase in mucosal and cutaneous (including oesophageal) candidiasis, but cases were mild or moderate in severity, non-serious, responsive to standard treatment and did not necessitate treatment discontinuation. Serious infections occurred in a small proportion of patients (0.015 serious infections reported per patient year of follow up). *Neutropenia:* Neutropenia was more frequent with secukinumab than placebo, but most cases were mild, transient and reversible. Rare cases of neutropenia CTCAE Grade 4 were reported. *Hypersensitivity reactions*: Urticaria and rare cases of anaphylactic reactions were seen. *Immunogenicity:* Less than 1% of patients treated with Cosentyx developed antibodies to secukinumab up to 52 weeks of treatment. *Other Adverse Effects:* The list of adverse events is not exhaustive, please consult the SmPC for a detailed listing of all adverse events before prescribing. **Legal Category:** POM. **MA Number & List Price:** PLGB 00101/1205 – 75 mg pre-filled syringe x 1 - £304.70; PLGB 00101/1029 - 150 mg pre-filled pen x2 £1,218.78; PLGB 00101/1030 - 150 mg pre-filled syringe x2 £1,218.78; PLGB 00101/1198 – 300 mg pre-filled pen x 1 £1218.78. **PI Last Revised:** June 2023. Full prescribing information, (SmPC) is available from: Novartis Pharmaceuticals UK Limited, 2nd Floor, The WestWorks Building, White City Place, 195 Wood Lane, London, W12 7FQ. Telephone: (01276) 692255.

UK | 290802 | June 2023

Adverse Event Reporting:

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Novartis via uk.patientsafety@novartis.com or online through the pharmacovigilance intake (PVI) tool at www.novartis.com/report.

If you have a question about the product, please contact Medical Information on 01276 698370 or by email at medinfo.uk@novartis.com