Alimentary Tract

Rates, predictive factors and effectiveness of ustekinumab intensification to 4- or 6-weekly intervals in Crohn's disease

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ABSTRACT

Background: The UNITI trial reports efficacy of ustekinumab (UST) dose intensification in Crohn's disease (CD) from 12- to 8-weekly, but not 4-weekly. We aimed 1) to assess the cumulative incidence of UST dose intensification to 4- or 6-weekly, 2) to identify factors associated with dose intensification, and 3) to assess the effectiveness of this strategy.

Methods: We performed a retrospective, observational cohort study in NHS Lothian including all UST treated CD patients (2015–2020).

Results: 163 CD patients were treated with UST (median follow-up: 20.3 months [13.4–38.4]), of whom 55 (33.7%) underwent dose intensification to 4-weekly (n = 50, 30.7%) or 6-weekly (n = 5, 3.1%). After 1 year 29.9% were dose intensified. Prior exposure to both anti-TNF and vedolizumab (HR 9.5; 1.3–70.9), and concomitant steroid use at UST start (HR 1.8; 1.0–3.1) were associated with dose intensification. Following dose intensification, 62.6% patients (29/55) remained on UST beyond 1 year. Corticosteroid-free clinical remission was achieved in 27% at week 16 and 29.6% at last follow-up.

Conclusion: One third of CD patients treated with UST underwent dose intensification to a 4- or 6-weekly interval within the first year. Patients who failed both anti-TNF and vedolizumab, or required steroids at initiation were more likely to dose intensify.

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1. Introduction

Ustekinumab (UST) is a fully human IgG1 monoclonal antibody targeting the shared p40 subunit of interleukin-12 (IL-12) and IL-23. It is approved in patients with moderate to severe Crohn's disease (CD) [1] and ulcerative colitis [2]. The approved dose is a weight-based infusion (6 mg/kg) for the first dose, followed by subcutaneous injections of 90 mg every 8 or 12 weeks. Whilst the UNITI phase 3 programme demonstrated efficacy and safety of UST in CD patients compared to placebo, 15–35% of the patients still developed loss of response in the first three years after UST initiation [3–5].

For CD patients treated with anti-TNF maintenance therapy, a dose–response relationship has been demonstrated with higher drug levels associated with biochemical remission [6,7]. Indeed, dose intensification or interval shortening is typically recommended in patients who have lost response to optimise therapeutic drug levels [8]. A similar dose-response relationship may apply to

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biological therapy with vedolizumab [9] and UST [10]. Indeed, 20% of the patients who lost response on 12-week UST maintenance therapy in IM-UNITI, recaptured response after dose intensification to an 8-week interval [1]. In both our experience and reported real-world literature, most patients with CD starting on UST have had prior anti-TNF therapy and commence maintenance at the 8-weekly regimen. Where these patients lose response to 8-weekly UST, a dose interval reduction to 4- or 6 weekly might be an effective strategy. However, this was not assessed in randomized clinical trials.

Uncontrolled data suggest UST dose intensification to a 4- or 6-weekly interval may be effective and safe in some IBD patients [3,11–16]. However, most of these studies are limited by small sample size, lack of long-term follow-up and selection bias. Furthermore, most studies have included only those patients who underwent UST dose intensification and therefore cannot identify those patients at increased risk for dose intensification overall.

In this study, we aimed to assess the cumulative incidence of UST dose intensification to a 4- or 6-weekly interval and to identify factors associated with dose intensification. Subsequently, we aimed to investigate the effectiveness and safety of this strategy.

2. Methods

2.1. Study design and outcomes

We performed a retrospective observational cohort study in NHS Lothian (Scotland) aiming (1) to assess the cumulative incidence of UST dose intensification to a 4- or 6 weekly interval in CD patients, (2) to identify factors associated with dose intensification, and (3) to evaluate the effectiveness and safety of this strategy. NHS Lothian provides universal, free at point of care, healthcare for a population of 912,490 people (estimate mid 2020) covering a geographically defined area of 1724 km2 (Edinburgh city, Mid Lothian, West Lothian and East Lothian) [17]. Secondary care is delivered by four hospitals (the Western General Hospital [principal IBD unit], the Royal Infirmary of Edinburgh, St John’s Hospital and the Royal Hospital for Sick Children). More than 8000 patients in NHS Lothian are diagnosed with IBD [18,19].

The primary endpoint to assess effectiveness was UST drug persistence. Secondary endpoints included corticosteroid-free clinical remission, cumulative corticosteroid-free clinical remission, biochemical remission (CRP \(< 5\) mg/l), faecal biomarker remission (faecal calprotectin [FCAL] \(< 250\) μg/g) [6], and safety parameters (adverse events). Corticosteroid-free clinical remission was defined as a Harvey Bradshaw Index (HBI) \(< 4\) without receiving corticosteroids and was measured at week 16 following dose intensification and at the end of last follow-up [20,21].

2.2. Patients

Lloyds Pharmacy Clinical Homecare provides UST for all NHS Lothian [18] IBD patients and prospectively registers all UST prescriptions. We performed a search in this database to identify all IBD patients in NHS Lothian who were on UST treatment between 22 January 2015 and 28 October 2020. An additional cross-check was performed with the Lothian IBD Biologics Database, containing all biological prescriptions for IBD patients since 1 August 2009 [18]. All adult patients \(\geq 18\) years with a confirmed CD diagnosis and with at least one dose of UST were eligible for inclusion.

2.3. Data collection

Patient demographics and IBD characteristics were extracted from electronic medical health records (TrakCare®). We collected the following data: sex, medical history, smoking history, body mass index (BMI), IBD type, age at IBD diagnosis, disease extent and phenotype according to the Montreal classification, previous IBD-related surgery, and both previous and ongoing exposure to IBD-related medical therapies. UST start date and dose were recorded as well as the dates and reasons for dose intensification. Reasons were classified into: the absence of corticosteroid-free clinical remission, biochemical disease activity (CRP \(> 5\) mg/l and/or FCAL \(> 250\) μg/g measured within 3 months before dose intensification), and/or active inflammation during endoscopy and/or MRI (measured within 6 months before dose intensification). In addition, UST stop dates and reasons for treatment discontinuation were recorded. Primary non-response was defined as lack of clinical or biochemical improvement after at least 8 weeks of induction therapy, requiring UST discontinuation. Secondary loss of response was defined as initial clinical response to induction therapy but subsequent loss of response to maintenance therapy, requiring UST discontinuation [22]. To assess effectiveness of UST we extracted clinical scores (HBI), CRP and FCAL at start of UST and during follow-up. All adverse events during follow-up were documented. A serious adverse event was defined as an adverse event leading to UST suspension or discontinuation, hospitalisation, or death.

2.4. Statistics

All analyses were performed with IBM SPSS statistical software package version 25 [Armonk, NY]. We used descriptive statistics to describe baseline characteristics. Continuous variables are expressed as medians and interquartile range or mean and standard deviation, depending on distribution and were analysed with a Student t-test or Mann-Whitney U test as appropriate. Categorical variables were reported as frequencies and were analysed with chi-square / Fisher’s exact test.

Dose intensification curves were established with cumulative incidence Kaplan Meier curves. Time-to-event was calculated from the start UST on an 8-weekly interval to dose-intensification to a 4- or 6-weekly interval. Patients were censored at the end of follow-up, which was defined as the last data collection point or patients’ death. We performed explorative analyses with univariable and multivariable Cox regression analyses to identify factors independently associated with dose intensification. In case of a p-value of \(< 0.1\) in univariable analysis, variables were included in the multivariable analysis. A p-value of \(< 0.05\) was considered statistically significant.

Drug persistence was evaluated with Kaplan Meier curves. Corticosteroid-free clinical, biochemical, and faecal biomarker remission were analysed as categorical variables. Data were collected as close to dose intensification, at week 16 (\(\pm 6\) weeks), and at last follow-up. We performed an intention-to-treat analysis considering patients who discontinued UST as non-responders to obtain a conservative estimate of outcomes. Remission rates were compared with baseline using McNemar’s test for comparisons of paired nominal data.

2.5. Ethics

This work was considered a service evaluation/audit as all data were collected as part of routine clinical care. Therefore, no written consent or formal ethical approval was necessary as per departmental policy and Health Research Authority guidance.

3. Results

3.1. Patients

163 CD patients who were treated with UST in NHS Lothian were included. 71 patients (43.6%) were male with a median CD
duration of 9.5 years (4.8 – 17.1) before start of UST (Table 1). Most patients had ileocolonic (L3) disease distribution (47.9%) and 28.2% (46/163) had perianal disease. 21/163 patients (12.9%) were biological naïve, whereas 142 patients (87.1%) were previously treated with one (anti-TNF or vedolizumab; n = 100, 61.3%) or two types of biologics (anti-TNF and vedolizumab; n = 42, 25.8%). Most patients were started on an 8-weekly UST dose interval (129/163, 79.1%; Table 2, Supplementary Figure 1). Of 34 patients who started on a 12-weekly UST interval, 15 (44.1%) underwent dose intensification to an 8-weekly interval after median 7.8 months (4.0 – 18.6). 23.3% (38/163) were concomitantly treated with systemic corticosteroids at start of UST. The median duration of follow-up after start of UST was 20.3 months (13.4 – 38.4), corresponding with 255 person years of follow-up (PYF).

### 3.2. Dose intensification to 4- or 6-weekly

Of 163 patients, 55 (33.7%) underwent dose intensification to a 4-weekly (n = 50, 30.7%) or 6-weekly (n = 5, 3.1%) UST interval. 45/50 patients were previously treated on a 12-weekly interval and underwent dose intensification twice (initially to an 8-weekly and subsequently to a 4-weekly interval, Supplementary Figure 1). Median time to dose intensification was 6.1 months (3.9 – 11.0) and after 1 year 29.9% were escalated to a 4- or 6-weekly dose interval (Fig. 1). Indications for UST intensification included absence of steroid-free clinical remission (n = 47, 85.6%), biochemical disease activity (CRP > 5 mg/l; n = 34, 61.8%; FCAL > 250 µg/g; n = 36, 65.5%), active disease during endoscopy (n = 8, 14.5%) and/or active disease seen on MRI (n = 27, 49.1%). Dose intensification was driven by clinical disease activity alone in 5/55 patients (9.0%), whereas 50/55 patients (91.0%) underwent UST intensification based on at least one objective marker of inflammation (CRP / FCAL / active inflammation during endoscopy / MRI). 11/55 patients (20%) had active perianal disease contributing to dose intensification, of whom 3 patients had disease limited to the perianal region only. The median duration of follow-up after dose intensification was 16.9 months (8.9 – 27.3).

### 3.3. Factors associated with dose intensification to a 4- or 6-weekly interval

Patients who underwent dose intensification were diagnosed with CD at a younger age (p = 0.020), and had more often penetrating (p = 0.001) and perianal disease (p = 0.009; Table 1). They were less often biological naïve and had more frequently prior treatment with both anti-TNF and vedolizumab (p < 0.001). Furthermore, patients who underwent dose intensification were more often started on an 8-weekly dose interval (p = 0.002) with concomitant use of steroids (p = 0.042).

Multivariable analysis showed that prior exposure to both anti-TNF and vedolizumab (HR 9.5; 1.3 – 70.9) as well as concomitant steroid use (HR 1.8; 1.0 – 3.1) were independently associated with dose intensification. These factors may reflect more severe, treatment refractory CD without any licensed treatment options left for these patients. After 1 year, 47.2% of the patients with prior exposure to both anti-TNF and vedolizumab were escalated to a 4- or 6-weekly dose interval versus 5.0% in the biological naïve group (Fig. 1).


Table 2
Details of ustekinumab dosing and follow-up.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total cohort (n = 163)</th>
<th>Patients who had dose intensification to 4- or 6-weekly intervals (n = 55)</th>
<th>Patients who did not have dose intensification to 4- or 6-weekly intervals (n = 108)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ustekinumab dose at start, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>- 8 weekly intervals</td>
<td>129 (79.1)</td>
<td>51 (92.7)</td>
<td>78 (72.2)</td>
<td></td>
</tr>
<tr>
<td>- 12 weekly intervals</td>
<td>34 (20.9)</td>
<td>4 (7.3)</td>
<td>30 (27.8)</td>
<td></td>
</tr>
<tr>
<td>Concomitant IBD therapy at start</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ustekinumab treatment, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Steroids</td>
<td>38 (23.3)</td>
<td>18 (32.7)</td>
<td>20 (18.5)</td>
<td>0.042</td>
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<td>- SASA</td>
<td>1 (0.6)</td>
<td>0</td>
<td>1 (0.9)</td>
<td>1.000</td>
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<td>- Immunosuppressant (thiopurine / methotrexate)</td>
<td>20 (12.3)</td>
<td>4 (7.3)</td>
<td>16 (14.8)</td>
<td>0.165</td>
</tr>
<tr>
<td>Ustekinumab dose intensification reasons, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Absence of steroid-free clinical remission</td>
<td>60 (36.8)</td>
<td>26 (47.3)</td>
<td>34 (31.5)</td>
<td>0.013</td>
</tr>
<tr>
<td>- CRP &gt; 5 mg/l</td>
<td>7.3 (4.9 – 16.7)</td>
<td>16.9 (6.9 – 21.3)</td>
<td>5.4 (3.8 – 9.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- FCAL &gt; 250 ug/g</td>
<td>11 (20.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Active inflammation during endoscopy</td>
<td>8 (14.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Active inflammation on MRI</td>
<td>27 (49.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Active perianal disease</td>
<td>20.3 (13.4 – 38.4)</td>
<td>26.4 (17.5 – 38.4)</td>
<td>16.9 (12.3 – 38.6)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Fig. 1. Dose intensification curve showing the proportion of Crohn's disease patients who underwent dose intensification to a 4- or 6-weekly UST interval. The bold black line shows dose intensification in the total cohort, whereas other lines represent subgroups based on the number of previous biological drug classes.

3.4. Drug persistence

Of 163 patients, 60 patients (36.8%) discontinued UST during a follow-up time of 20.3 months (13.4 – 38.4). Median time to UST discontinuation was 7.3 months (4.9 – 16.7) and 76.9% remained on UST beyond 1 year (Fig. 2A). Reasons for treatment discontinuation included primary non-response (25/163, 15.3%), secondary loss of response (31/163, 19.0%), adverse events (2/163, 1.2%), and rheumatological disease necessitating treatment with another biological (2/163, 1.2%).

83.6% of the patients who underwent dose intensification to a 4- or 6-weekly interval remained on UST beyond 1 year following UST initiation versus 73.4% in the group without dose intensification (Fig. 2A). Of 55 patients who underwent dose intensification...
26 patients discontinued UST due to active CD after median 5.2 months (3.5–12.6) since dose intensification (median 16.9 months [6.9–21.3] since UST start). One year after dose intensification, 62.6% remained on UST (Fig. 2B). No licensed treatment options were left in 12/29 patients who remained on UST (Supplementary Table 1).

3.5. Next treatment line following UST

The majority of patients who discontinued UST were subsequently treated with vedolizumab (24/60, 40%) or anti-TNF (15/60). 11/60 patients (18.3%, of whom 7 were on a 4-weekly interval when UST was discontinued) received non-licensed treatment with tofacitinib, risankizumab, thalidomide, tacrolimus, filgotinib, or autologous stem-cell transplantation. IBD-related surgery was performed in 8/60 patients (13.3%; 6/8 were on 4-weekly UST) following UST discontinuation. Two patients (2/60, 3.3%) discontinued UST due to adverse events and continued without any further IBD treatment.

3.6. Outcomes of dose intensification

At dose intensification, 14.5% of the patients (8/55) were in corticosteroid-free clinical remission versus 27.0% (10/37, p = 0.008; missing values: n = 18) at week 16 and 29.6% (16/54, p = 0.077; missing values: n = 1) at last follow-up after median 8.9 months (4.3–14.8; Fig. 3A). Of 46 patients who were not in corticosteroid-free clinical remission at dose intensification, 51.1% achieved corticosteroid-free clinical remission in the first year after UST dose intensification (Fig. 3B). The limited availability of CRP and FCAL data in predefined time windows did not allow us to reliably compare biochemical remission rates.

29 patients remained on UST at last follow-up, of whom 15 patients were in corticosteroid-free clinical remission and 13 were not (missing value: n = 1). In addition, 14/29 patients (48.2%) were not in biochemical remission (CRP ≤5 mg/l) and 13/29 patients (44.8%) were not in faecal biomarker remission (FCAL ≤250 ug/g; Supplementary Table 1). No licensed treatment options were left...
in 5/13 patients (38.5%) who remained on UST and were not in corticosteroid-free clinical remission.

Dose de-escalation took place in 1/55 patients after 16 months due to clinical and biochemical remission (FCAL < 20 μg/g; CRP = 1 mg/l). At the end of follow-up, this patient was still in deep remission on an 8-weekly UST interval.

3.7. Safety

Fourteen adverse events were reported in 12 patients whilst being treated with UST on an 8- or 12-weekly interval, resulting in an adverse event rate of 8.3 per 100 PYF. Adverse events included skin reactions, infections, arthralgia, headache, and cardiac failure (all events occurred ≤5; exact numbers not reported to avoid the use of personally identifiable information which can be traced back to a person). Of these adverse events, 5 were classified as severe of whom 2 patient discontinued UST.

Five adverse events (including infections and headache) were reported in 5 patients being treated with UST on a 4- or 6-weekly interval. This resulted in a comparable adverse event rate of 6.0 per 100 PYF (p = 0.54). One patient with recurrent infections required temporary discontinuation of UST and was classified as having a severe adverse event.

4. Discussion

In this retrospective cohort study, we showed that approximately one third of CD patients treated with UST underwent dose intensification to a 4- or 6-weekly interval within the first year. Patients who failed two or more biologics as well as those with concomitant steroid use were more likely to dose intensify. After dose intensification, corticosteroid-free clinical remission was achieved in 27% at week 16 and 29.6% at last follow-up. Of 29 patients who remained on UST, 13 (44.8%), 14 (48.2%) and 13 (44.8%) patients were not in corticosteroid-free clinical, biochemical and/or faecal biomarker remission, respectively. These patients represent a very refractory group of CD patients with often no licensed treatment options available.

We demonstrated that after 1 year 29.9% of UST patients on an 8-weekly dose interval were escalated to a 4- or 6-weekly interval, which is in line with previous literature. Two recent meta-analysis reported annual UST dose escalation rates (including escalation to 8-weekly intervals, and/or IV reinduction) of 20–25% amongst primary responders [15,23]. Of 464 CD patients in the multicentre SUSTAIN study, 100 (21.6%) underwent dose intensification to a 4- or 6-weekly interval (n = 94) or IV reinduction (n = 6) within a median study follow-up of 15.5 months [24]. Another large single centre study reported dose intensification in 110 of 506 CD patients (21.7%) after median 7.5 months [14]. Smaller, older studies (2016 - 2018) have shown 4/6-weekly dose escalation rates between 11% and 22% after a median of 10–14 months follow-up [25–27]. Since less UST experience was available by then, dose escalation might have been more uncommon. Our observation that approximately one third of UST treated CD patients is on a 4- or 6-weekly interval after one year is a striking, especially since an 8- or 12-weekly interval is recommended [28]. The absence of licensed therapeutic options in many of these highly refractory CD patients may have contributed to this clinical practice, underlining the need for new IBD therapies.

UST dose intensification appears to be effective, although firm conclusive data are still lacking. We reported a corticosteroid-free clinical remission rate of 29.6% at last follow-up (median follow-up time after dose intensification: 16.9 months), which is in line with data from a French cohort (corticosteroid-free clinical remission: 26% at last follow-up after a median follow-up of 8.2 months) [3]. Similarly, week 16 corticosteroid-free clinical remission rates in our study (27%) were comparable with those from a multicentre study (18%, p = 0.70) [13]. In addition, comparable cumulative corticosteroid-free clinical remission percentages were found in our study (51%) and a cohort study in a tertiary referral centre (55%) [11]. A systematic review and meta-analysis (n = 8 studies + 7 abstracts) evaluating effectiveness of dose-escalation demonstrated that 55% of patients achieved clinical response, 40% corticosteroid-free clinical remission (51% in our study), 61% endoscopic response and 21% CRP normalisation [15]. However, similar to our study the retrospective nature of included studies resulted in absence of systematically collected data on predefined time- and endpoints. Consequently, reported endpoints of this meta-analysis do not cover timing and sustainability of remission / response, hampering the interpretation for use in daily clinical practice. A recent post-hoc analysis from STARDUST, an RCT comparing treat-to-target versus standard of care in UST treated CD patients, reported no major differences in clinical and endoscopic endpoints between patients who intensified to 4-weekly and those who stayed on 8-weekly [29]. More prospective UST observational and/or controlled trials with predefined short- and long-term endpoints following dose escalation are needed to further progress in this area. As such,
CD-POWER (NCT03782236), a phase 3b RCT, investigates the efficacy of a single IV reinduction dose (6 mg/kg) in CD patients with secondary loss of response to 8-weekly UST.

Some data show that higher serum concentrations are associated with better outcomes of UST [10,30]. However, this has not made it through to routine clinical practice and as such data are lacking for our cohort. Post-hoc analyses of the UNITI-trials reported strong associations between UST concentrations and efficacy outcomes for both the induction and maintenance phase [10]. Similarly, a cohort study demonstrated a dose response for endoscopic and biomarker response. Patients with an UST trough concentrations >4.5 μg/ml during maintenance at week 26 had significantly more often endoscopic response and a lower CRP, whilst higher drug concentrations were not associated with increased adverse events [30]. Whilst we don’t have any direct evidence, this may support dose intensification.

The most optimal timing for UST dose intensification remains unclear, particularly given the high costs associated with such a strategy, versus switching to another class of drug. The major predictor for dose intensification in our study was failing of two or more biologics. For many of these patients there are presently no other licensed treatment options available. This will change with the advent of newer therapies for Crohn’s disease including p19 and selective JAK1 inhibitors [31]. However, within 2 years UST biosimilars will also be available and the cost benefit analyses will shift substantially as we have seen with anti-TNF drugs.

Strengths of this study included the availability of data for both dose intensified patients as well as for the total cohort allowing us to establish a cumulative dose intensification curve and the identification of risk factors for dose escalation. Substantial evidence supporting the validity of our data is the comparable UST persistence after 1 year compared with the SEAVUE data (76.9% vs 84.8%) [32]. Nevertheless, some limitations should be addressed. First, this includes the retrospective study design with its inherent risk of bias, variable follow-up and incompleteness of data. For example, CRP, FCAL and endoscopic endpoints were not systematically collected at predefined time points not allowing us to analyse biochemical and endoscopic remission in a reliable way. Second, UST drug levels substantiating dose escalation were not available. Finally, the cohort was heterogeneous without predefined criteria for dose escalation and different escalation regimens. However, this reflects real-world practice, allowing direct translation of results into daily clinical practice.

In conclusion, one third of CD patients treated with UST underwent dose intensification to a 4- or 6-weekly interval within the first year. Patients who failed two or more biologics were more likely to dose intensify. These are a very refractory group of CD patients, of whom many have no licensed treatment options available.

Conflict of interest

Lauranne Derikx has served on an advisory board for Sandoz and as a speaker for Janssen.

Spyros Siakavellas has received speaker fees from Pfizer and Janssen.

Nikolas Plevris has served as a speaker for Janssen, Takeda and Pfizer.

Beatriz Gros has served as a speaker for Abbvie and Galapagos.

Colin Noble has served on an advisory board for Galapagos.

Gareth-Rhys Jones has served as a speaker for Takeda, Janssen, Abbvie and Ferrigno.

Charlie Lees has acted as a consultant to Abbvie, Janssen, Takeda, Pfizer, Galapagos, BMS, Pharmacosmos, GSK, Gilead, Topi-vert, Vifor Pharma, Celltrion, Dr Falk, Oshi Health, Trellus Health and Iterative Scopes; he has received speaking fees and travel sup-

port from Pfizer, Janssen, Abbvie, Galapagos, Fresnius Kabi, Takeda, Shire, Ferrigno, and Dr Falk.

None of the other authors reported any conflicts of interest.

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Supplementary materials


References


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