Lupus nephritis (LN) is one of the most severe manifestations of systemic lupus erythematosus (SLE), an autoimmune condition with unclear etiology that disproportionately affects women. The current therapies used for the treatment of LN are primarily older, genericized agents that are prescribed off-label. As a result, when selecting treatment for LN patients, physicians have a limited choice of agents to prescribe and have no alternative but to use drugs with unfavorable safety profiles; they also run into reimbursement obstacles due to the off-label nature of the most potent LN therapies, and finally, must struggle with treating those patients who have failed to respond adequately to the available agents.
What is past is prologue

For many years, drug development for SLE — both extra-renal disease and LN — lagged behind that of the larger autoimmune indications such as RA and psoriasis. However, as these two indications were becoming saturated with a plethora of efficacious and fairly safe, branded — and now biosimilar — treatments, drug developers turned their eyes to SLE. As the result of these efforts, in 2011, GSK’s BLyS/BAFF inhibitor, Benlysta (belimumab), became the first drug approved for SLE in the United States in more than 50 years; it was also approved in Europe later that year. However, since then, several emerging therapies have failed Phase III trials in extra-renal SLE (i.e., Eli Lilly’s tabalumab, UCB’s epratuzumab, and Anthera’s blisibimod), disheartening physicians and discouraging the lupus community at large, a group that had previously hoped Benlysta would usher in a new era of drug approvals.

The situation is even bleaker in LN — no drugs are approved specifically for this SLE subpopulation; Benlysta’s FDA and EMA labels explicitly exclude patients with active LN, and no new Phase III trial results (positive or negative) have been announced since the high-profile failure of Roche/Biogen’s Rituxan/MabThera (rituximab) in LN in 2009. As a result, the level of unmet need in LN remains high and novel, approved therapies capable of providing better induction and/or maintenance outcomes than the currently used off-label agents, improved safety, and/or efficacy in treatment-refractory patients are desperately sought by physicians (for more insights on unmet needs in LN please see DRG’s 2017 Lupus Nephritis Unmet Need content).

Table 1: Select Clinical Trial Failures in SLE/LN

<table>
<thead>
<tr>
<th>Compound</th>
<th>Marketing Company</th>
<th>MOA</th>
<th>Indication</th>
<th>Trial Stage and Trial ID</th>
<th>Key Takeaways</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tabalumab</td>
<td>Eli Lilly</td>
<td>B-cell modulator (targets BLyS/BAFF)</td>
<td>SLE (excluding LN)</td>
<td>Phase III NCT01196091 NCT01205438</td>
<td>Tabalumab failed its first Phase III trial, but in the second Phase III trial, the higher dose met the primary end point (measured with SRI-5). Tabalumab’s MOA is similar to that of Benlysta and thus is proven to work in SLE; interviewed KOLs suggest that more-frequent dosing or higher doses may have demonstrated better outcomes.</td>
</tr>
<tr>
<td>Epratuzumab</td>
<td>UCB</td>
<td>B-cell modulator (targets CD22)</td>
<td>SLE (excluding LN)</td>
<td>Phase III NCT01262365 NCT01261793</td>
<td>Epratuzumab failed both Phase III trials in SLE (BICLA used as the primary end point). High placebo-response rate, suboptimal dosing, and high use of corticosteroids were proposed as possible reasons for the trial failure. However, some KOLs, instead, question epratuzumab’s MOA as relevant for SLE.</td>
</tr>
<tr>
<td>Rituxan/MabThera (rituximab)</td>
<td>Biogen/Roche/Genentech</td>
<td>B-cell modulator (targets CD20)</td>
<td>SLE (excluding LN)</td>
<td>Phase II/III NCT00137969</td>
<td>The drug failed to meet the primary end point (measured with BILAG), although a possible signal was observed in a subgroup analysis. Among the most likely reasons for the trial failure are (1) the patient population recruited for the trial was different from that in which rituximab had been used off-label in clinical practice, and (2) the primary outcome measure was too strict.</td>
</tr>
</tbody>
</table>

Continued on next page
Table 1: Select Clinical Trial Failures in SLE/LN (Continued)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Company</th>
<th>Type of Modulator</th>
<th>Disease</th>
<th>Phase</th>
<th>Trial Identifier</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituxan/MabThera (rituximab)</td>
<td>Biogen/Roche/G-</td>
<td>B-cell modulator (targets CD20)</td>
<td>LN</td>
<td>III</td>
<td>NCT00282347</td>
<td>The Phase III trial failed, but a numerical difference was seen between rituximab and placebo in the percentage of patients who achieved complete renal response. It is likely that the trial was underpowered and too short in duration (one year) to demonstrate a statistically significant difference.</td>
</tr>
<tr>
<td>Ocrevus (ofatumumab)</td>
<td>Biogen/Genentech</td>
<td>Antibody (targets B-cells)</td>
<td>LN</td>
<td>IIb</td>
<td>NCT00119678</td>
<td>Ocrevus failed to meet the primary end point of the trial and demonstrate reduction in the number of new SLE flares. However, in the post hoc analysis, a reduction in the number of severe flares was observed. The trial may have failed because milder flares (which are ambiguous to score) were included in the primary outcome measure.</td>
</tr>
<tr>
<td>Orencia (abatacept)</td>
<td>Bristol-Myers</td>
<td>T-cell modulator (targets co-stimulation)</td>
<td>SLE (excluding LN)</td>
<td>IIb</td>
<td>NCT00119678</td>
<td>Ocrevus failed to meet the primary end point of the trial and demonstrate reduction in the number of new SLE flares. However, in the post hoc analysis, a reduction in the number of severe flares was observed. The trial may have failed because milder flares (which are ambiguous to score) were included in the primary outcome measure.</td>
</tr>
<tr>
<td>Orencia (abatacept)</td>
<td>Bristol-Myers</td>
<td>T-cell modulator (targets co-stimulation)</td>
<td>LN</td>
<td>II/III</td>
<td>NCT00430677</td>
<td>Ocrevus failed to meet the primary end point of the trial (time to confirmed complete renal response), likely because the definition of complete response was too strict. When a different definition of complete response (as defined in rituximab Phase III trial [NCT00282347]) was used in a post hoc analysis, abatacept demonstrated efficacy. The drug is now in a Phase III trial in patients with LN.</td>
</tr>
</tbody>
</table>

Sources: clinicaltrials.gov, company reports and websites, press releases.

To develop or not to develop: that is the question

One of the reasons why SLE is frequently overlooked by drug developers is because the disease is notoriously difficult to target owing to its complex pathophysiology and heterogeneous patient population. Bringing a LN drug to the market is particularly challenging because of the lack of well-defined end points and up-to-date guidance(s) to aid with development and regulatory processes, in addition to the fact that there is currently no clear pathway for drug approval — because no drugs have ever been approved for LN in the United States or Europe. Furthermore, the relatively low prevalence of the disease diminishes the attractiveness of this indication for drug developers in the autoimmune space, who are more apt to target highly prevalent indications such as RA or psoriasis.

Despite what seems like an unfavorable drug development environment, winning approval for a new LN drug would likely mean enjoying several benefits that the larger autoimmune markets cannot provide. Firstly, any agent which wins regulatory approval for LN, offering attractive risk/benefit profile and designed to replace therapies currently used to treat LN, is likely to enjoy very limited competition from the toxic, off-label treatments prescribed. Similarly, a new agent intended for use as an add-on to the current SOC, although potentially seeking to conquer a slightly smaller population of LN patients, will initially face virtually no competition.
“For lupus nephritis, there is really no competition. Anyone with a small molecule or biologic that’s quick-acting and very efficacious will have the market almost to themselves. Even for nonrenal lupus, the market is not crowded. We have belimumab that works really only well in people who have low complement and high anti-DNA antibodies. Again, the market is wide open. I think companies should still be very encouraged about lupus, although obviously the fact that both Eli Lilly and UCB had their Phase III trials turn out to be complete disappointments gave lupus a bad name.”

—Rheumatologist, United States

Secondly, because LN is a severe disease— inability to control renal inflammation will result in ESRD and ultimately death—and a disease with a high level of unmet need, new efficacious (and reasonably safe) treatments are poised to enjoy an easier P&R environment compared with the more-crowded immune markets. In RA, for example, the well-established TNF-α inhibitors, Enbrel and Humira, dominate the market, enjoying high physician familiarity and favorable formulary coverage, thereby making it extremely difficult for newer branded agents to compete. Also, the availability of TNF-α biosimilars will further constrain the pricing environment in the RA market. In contrast, the SLE (including LN) market will be more open to new therapies and more resistant to biosimilar price erosion, because Benlysta will remain the key pricing benchmark for novel SLE/LN agents. Thirdly, due to the relatively low prevalence of LN, historically some drug developers were able to obtain orphan disease designations from the FDA for their candidates in development for LN. If successfully granted, such an orphan disease designation could aid with the development process for a new LN candidate and help to shield the agent from generic/biosimilar competition. Finally, similar to other autoimmune conditions, LN is a chronic disease that relies on prolonged maintenance treatment to prevent debilitating and costly disease flares, thus allowing companies to recoup the cost of development and make a profit.

### Table 2: Select Agents in the LN Pipeline

<table>
<thead>
<tr>
<th>Compound</th>
<th>Marketing Company</th>
<th>MOA</th>
<th>Status in LN and Trial ID (Estimated Primary Completion Date)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benlysta (belimumab)</td>
<td>GlaxoSmithKline</td>
<td>B-cell modulator (BLYS/BAFF inhibitor)</td>
<td>Phase III NCT01639339 (July 2019)</td>
</tr>
<tr>
<td>Orencia (abatacept)</td>
<td>Bristol-Myers Squibb</td>
<td>T-cell modulator</td>
<td>Phase III NCT01714817 (November 2016)</td>
</tr>
<tr>
<td>Orelvo (voclosporin)</td>
<td>Aurinia Pharmaceuticals</td>
<td>Calcineurin inhibitor</td>
<td>Phase III NCT03021499 (December 2019)</td>
</tr>
<tr>
<td>Gazyva/Gazyvaro (obinutuzumab)</td>
<td>Roche</td>
<td>B-cell modulator</td>
<td>Phase II NCT02550652 (August 2019)</td>
</tr>
<tr>
<td>Anifrolumab</td>
<td>MedImmune (subsidiary of AstraZeneca)</td>
<td>IFN-α inhibitor</td>
<td>Phase II NCT02547922 (September 2019)</td>
</tr>
</tbody>
</table>

Source: clinicaltrials.gov, last accessed May 15, 2017
Biologics in the LN pipeline: we know what they are, but know not what they may be

Despite the challenges in development and the failures to date, pharmaceutical companies continue pursuing LN labeling, with the expectation of capturing the market and snatching the first-to-market advantage. There are two biologics in Phase III development for LN, BMS’s T-cell modulator, abatacept (marketed as Orencia in RA), and Benlysta. Both agents have a long history of development in lupus. Abatacept previously failed a Phase IIb trial in extra-renal SLE and a Phase II/III trial in LN — likely due to suboptimal trial design. Despite these failures, BMS decided to advance the drug into Phase III for LN, changing the design and the end points in the new Phase III trial. According to the website, clinicaltrials.gov, the trial had a primary completion date in November 2016, and thus, we expect topline data from the trial to be released soon. Unlike abatacept, Benlysta was successful in its Phase III trials in patients with extra-renal, extra-CNS SLE. However, the agent is viewed as only modestly efficacious by physicians, thus raising the question of whether either of these biologics can demonstrate significant efficacy in patients with LN. Another problem is that both abatacept and Benlysta are perceived by physicians as notoriously slow-acting, and as a result, even if approved for LN, are likely to be unsuitable as induction treatments.

The third biologic to keep an eye on is AstraZeneca’s IFN-α inhibitor, anifrolumab. Although only in Phase II for LN and with no data available in this subpopulation, in a Phase Ib trial in extra-renal SLE anifrolumab was able to achieve efficacy potentially superior to that of Benlysta (though with a small compromise in safety), raising a high level of enthusiasm from SLE experts. However, in order to evaluate the full potential of this agent in LN, efficacy and safety data from trials conducted specifically in LN are needed. The last but certainly not the least, is Roche’s CD20 inhibitor, Gazyva/Gazyvaro (obinutuzumab), a biobetter of Rituxan/MabThera, currently in a Phase II trial in patients with LN (no evaluable clinical trial data for the agent are available in SLE or LN, yet). Unlike Rituxan/MabThera — which according to the experts failed trials in SLE and LN due to the trial design issues and now is used off-label in SLE patients with severe organ involvement (including LN patients) — Gazyva/Gazyvaro stands a better chance to become approved for LN, learning from the failed Rituxan/MabThera trials, while being shielded from biosimilar competition. Importantly, if Gazyva/Gazyvaro can match Rituxan/MabThera’s fast onset of action, it will likely give the agent a competitive advantage against other emerging LN biologics discussed here, because it could then be used in both induction and maintenance stages of treatment. For more insights on biologics in development for LN please see DRG’s Systemic Lupus Erythematosus Disease Landscape and Forecast content.

What’s in a name? That which we call Orelvo

Previously, Aurinia Pharmaceuticals’ oral calcineurin inhibitor, Orelvo (voclosporin), was viewed by many as the pipeline underdog. Although the older agents from this class (e.g., tacrolimus) have been available for years, they have never been widely adopted by physicians treating SLE. This result is partially because of physicians’ skepticism regarding these off-label agents’ ability to promote long-term remission in SLE, and partially due to the perceived lack of efficacy in extra-renal disease, and unpleasant side effects. However, LN Phase II trial data for voclosporin published in 2016 showed that voclosporin may have greater potential than previously expected. In the induction phase of the trial, addition of voclosporin to the SOC (mycophenolate mofetil and corticosteroids) induced a treatment effect, defined as the percentage of patients who achieved complete renal response at 24 weeks, in 13% of patients. In the maintenance phase of the trial, twice as many patients in a low-dose voclosporin arm achieved a complete renal response at 48 weeks, compared with the SOC arm (49% vs. 24% of patients), which is a striking
achievement for a drug in development for LN. Also worth noting, the design of the trial incorporated mandatory corticosteroid sparing, which will be viewed highly positive by physicians.

Despite the encouraging data, some important questions remain to be answered. Additional data on durability of complete renal remission/response, preferably beyond the 48-week window, would be helpful to understand if treatment with voclosporin significantly improves a patient’s chance of staying in remission for a prolonged period of time. Also, because the primary end point of the trial was a composite outcome measure, it would be interesting to see if any particular component of this end point drove the observed response. Furthermore, safety data from the Phase III trial will be crucial to determine if physicians will widely adopt this add-on agent in LN, especially taking into consideration several deaths that occurred in the Phase II trial; these were largely viewed as treatment unrelated but are nevertheless unsettling to some physicians. It will also be important to learn if voclosporin has efficacy in reducing SLE disease activity in organs other than the kidneys, because LN patients typically have multiple organs affected by the disease. Although some data concerning this issue have been released by Aurinia in the past, more in-depth data from a larger Phase III are needed.

Will the addition of voclosporin to the current SOC become the new first-line treatment in LN? Assuming the drug is successful in Phase III, and demonstrates efficacy similar to that observed in the Phase II trial and a relatively clean safety profile, pricing of the drug will likely be key to the extent of its penetration into the LN market. If priced at too great premium, voclosporin will become vulnerable to competition from older off-label calcineurin inhibitors, which lack the robust clinical trial data in LN, but enjoy greater physician familiarity at a significantly lower cost.

For more insights on LN, SLE, Orelvo (voclosporin), Benlysta (belimumab), Orencia (abatacept), Rituxan/MabThera (rituximab), anifrolumab, Gazyva/Gazyvaro (obinutuzumab) — please contact us.

Notes

1. In the United States, Benlysta is approved for the treatment of adult patients with active, autoantibody-positive, SLE without severe active LN or severe active CNS manifestations.
2. In this trial, complete renal remission is a composite outcome measure that includes UPCR, eGFR, and a corticosteroid sparing metric.

Abbreviations

- BICLA: The BILAG-Based Composite Lupus Assessment
- BILAG: The British Isles Lupus Assessment Group
- CNS: Central nervous system
- eGFR: Estimated glomerular filtration rate
- ESRD: End-stage renal disease
- EU: Europe
- FDA: Food and Drug Administration
- IFN: Interferon
- LN: Lupus nephritis
- MOA: Mechanism of action
- P&R: Pricing and reimbursement
- RA: Rheumatoid arthritis
- SLE: Systemic lupus erythematosus
- SRI: The SLE responder index
- SOC: Standard of care
- UPCR: Urine protein to creatinine ratio
- U.S.: United States

Continued on next page
About the Author:

**ELENA KOZHEMYAKINA, PH.D.,
SENIOR BUSINESS INSIGHTS ANALYST**

Elena Kozhemyakina, Ph.D., is a senior business insights analyst at Decision Resources Group, specializing in pharmaceutical market analysis of the immune system disorders with expertise in systemic lupus erythematosus, rheumatoid arthritis, asthma, and inflammatory bowel diseases. Prior to joining DRG, Dr. Kozhemyakina completed a postdoctoral fellowship at Harvard Medical School, where she investigated molecular mechanisms involved in limb patterning, cartilage formation and pathogenesis of osteoarthritis. She published multiple peer-reviewed papers focused on molecular signaling of developmental disorders.

About Us:

**UnMet Need Module**

DRG’s Unmet Need module helps you understand the areas for opportunity by exploring unmet need for an indication. With DRG’s Unmet Need module, you can assess surveyed physicians’ weightings of both clinical and non-clinical attributes that influence treatment decisions for specific diseases; assess current drug performance against treatment drivers and goals as rated by physicians in both the US and Europe; and identify the greatest unmet needs and profile their commercial potential.

**Disease Landscape & Forecast Module**

DRG’s Disease Landscape & Forecast (DL&F) module is a comprehensive source of vital disease-specific business and market intelligence. It provides world-class epidemiology, keen insights into current treatment paradigms, in-depth pipeline assessments, and multivariable market forecasts—all supported by detailed primary and secondary research conducted by analysts with deep indication- and therapy area expertise.

**Decision Resources Group**

Decision Resources Group offers best-in-class, high-value data, analytics, and insights products and services to the healthcare industry, delivered by more than 700 employees across 15 global locations. DRG companies provide the pharmaceutical, biotech, medical device, financial services, and payer industries with the tools, insights and advice they need to compete and thrive in an increasingly complex and value-based marketplace. DecisionResourcesGroup.com.

Have a question?

Email: Questions@TeamDRG.com